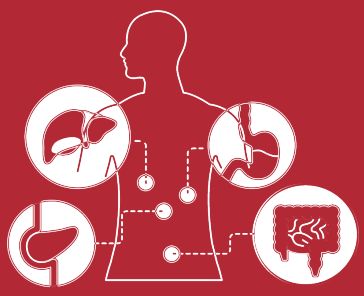
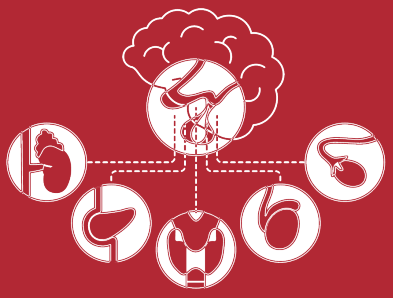
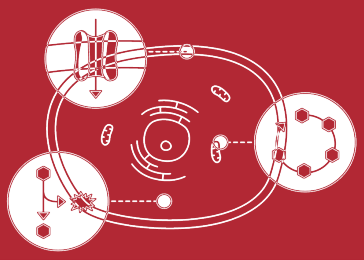
AGEM RETREAT

Abstract and Poster Book

2025







Gastroenterology

Endocrinology

Metabolism

Contents

Dear AGEM researchers,

Welcome to the 2025 Amsterdam Gastroenterology Endocrinology Metabolism (AGEM) retreat on April 3rd and 4th at the Bilderberg Hotel ‘t Speulderbos in Garderen.

We are proud to have over a hundred attendees this year. Eighty-five PhD-candidates and nine post docs have registered for this meeting, and most of them will present their research. In addition, the program contains inspiring lectures by scientists from outside our institute as well as fun and helpful workshops to develop new skills in your scientific career.

This program will give you a good impression of what fascinating research is being performed by your colleagues within the institute. The presentations (classical, elevator, and poster presentations) will certainly broaden your scientific horizon. The program contains both parallel and plenary sessions as well as shared breaks, lunches and dinner, followed by an exciting evening program. There is ample time to discuss projects and possible collaborations, also outside the scientific sessions. In fact, we strongly encourage you to approach the speakers and instigate such discussions!

The chair members will be strict regarding the time schedule. The front row of seats is reserved for the presenters from the ongoing session. Please take a seat at the front row, when the session of your presentation starts.

After dinner on Thursday, there will be a spectacular pubquiz where all your scientific and non-scientific knowledge can be put to the test. Afterwards, DJ Joff will treat us to a plethora of music to get you on your feet and dance the night away with us. The theme for the evening party is: *“Your favourite TV show/movie”*. Please dress accordingly, and let’s see how creative we get.

The next morning, we have organized an outdoor bootcamp for those early birds who enjoy raising their heart rates before breakfast, as well as an indoor yoga class for those would like to get refreshed and energized for the second day of the retreat.

We welcome you in Garderen and wish us all a successful meeting!
Nanne de Boer, Anita Boelen, and The AGEM Retreat Committee:

Valentina Bravo
Eva Dirkx
Diederick van Doorn
Mohammed Ghiboub
Kitty Latupeirissa
Omer Ozcan
Anne-Sophie Stroes
Maria Tretowicz
Kasper Vinten
Manon Wildenberg

Full program Thursday

Time	Session	Location
09:00-10:00	Registration & Store luggage	Entrance & Durven
10:00-10:15	Welcome and opening By AGEM directors and Diederick van Doorn	't Speuld
10:15-11:00	**Session A** Chaired by: Diederick van Doorn and Anne-Sophie Stroes	't Speuld
11:00-11:15	Tea / Coffee Break	Coffee corners / Grand cafe
11:15-12:00	Keynote speaker: Bart Takkenberg Alcohol and Society: Is drinking the new smoking?	't Speuld
12:00-12:15	Tea / Coffee Break	Coffee corners / Grand cafe
12:15-13:00	**Session B1** | Chaired by Kasper Vinten **Session B2** | Chaired by Omer Ozcan **Session B3** | Chaired by Kitty Latupeirissa **Session B4** | Chaired by Mohammed Ghiboub	Verwondering Levendig Fantasie Focus
13:00-13:45	Lunch	Restaurant
13:45-15:00	**Workshops** • Powerpoint karaoke • Sleep, light and the biological clock: How to optimize it for yourself and the relevance for your research • Action painting • How to: Presentations and public speaking • Organizing your PhD project: Lack of time or organization?	Focus Fantasie Daadkracht Verwondering Levendig
15:00-15:45	Forest walk	Outside
15:45-16:30	Out of the box speaker: Marjolijn Duijvenstein Reducing Medicine's Footprint Without Compromising Care	't Speuld
16:45-17:45	**Poster Session**	't Speuld
17:45-18:00	Relax / Dress up time & Check in (from 16:00)	
18:00-19:45	Dinner & dress up time	Restaurant
20:00-21:30	Evening entertainment: Pubquiz	't Speuld
21:30-01:30	Party DJ Joff | Theme: Favourite TV show / Movie	't Speuld

Full program Friday

Time	Session	Location
07:30-08:15	Morning activity Bootcamp | Yoga	Outside | Verwondering
08:15–09:15	Breakfast	Restaurant
09:15-10:00	**Session C** Chaired by: Kitty Latupeirissa and Kasper Vinten	't Speuld
10:00-10:45	Tea / Coffee Break & Check out of room	Coffee corners / Grand cafe
10:45-11:30	Keynote speaker: Georges Janssens A molecular tour through why we age	't Speuld
11:30-11:45	Tea / Coffee Break	Coffee corners / Grand cafe
11:45-12:30	**Session D1** | Chaired by Anne-Sophie Stroes **Session D2** | Chaired by Diederick van Doorn **Session D3** | Chaired by Maria Tretowicz **Session D4** | Chaired by Mohammed Ghiboub	Verwondering Levendig Fantasie Focus
12:30-13:30	Lunch	Restaurant
13:30-14:00	**Session E** Chaired by: Kitty Latupeirissa and Kasper Vinten	't Speuld
14:00-14:30	Lottery	't Speuld
14:30-15:00	Awards and closing talk By AGEM Directors, Anne-Sophie Stroes, and Diederick van Doorn	't Speuld

Speakers

Thursday

Bart Takkenberg | Keynote Speaker
Thursday April 3rd | 11:15-12:00 | 't Speuld

Bart Takkenberg is a hepatologist at the University Medical Center Amsterdam. He mainly treats patients with cirrhosis and complications of portal hypertension. In his outpatient clinic he sees many patients with cirrhosis as a result of excessive alcohol use. This is often a long-term and unintentional harmful drinking pattern, and the treatment of these patients is aimed at preventing further deterioration. This has both frustrated and puzzled him. What if these patients had never reached the stage of cirrhosis? What if their disease could have been prevented? How much would society benefit, and will there ever be legislation to prevent alcohol use? These questions motivated him to become involved in primary alcohol prevention. Since 2002, he has represented the Dutch Gastroenterology Association on the Alcohol Round Table. This is a discussion group formed by the State Secretary of Health and is part of the National Prevention Agreement from 2018.

Bart will talk about the interwovenness of alcohol in society and the role the alcohol industry plays in this. Is drinking the new smoking?

Marjolijn Duijvenstein | Out of the box speaker
Thursday April 3rd | 15:45-16:30 | 't Speuld

Dr. Marjolijn Duijvestein is a gastroenterologist at Radboud University Medical Center (Radboudumc) in Nijmegen, the Netherlands, where she leads the IBD team. Her research focuses on improving care for patients with Crohn's disease and ulcerative colitis, but her work extends beyond patient outcomes—she is also dedicated to making gastroenterology more sustainable. From conducting a Life Cycle Assessment (LCA) of colonoscopy procedures to advocating for greener clinical practices, she explores how research can drive environmental responsibility in healthcare. As an active member of United European Gastroenterology (UEG), she contributes to initiatives on sustainability and well-being in gastroenterology. During the retreat, Dr. Duijvestein will share her insights on integrating sustainability into medical research and practice, demonstrating how we can reduce the environmental footprint of healthcare while maintaining high-quality patient care.

Friday

Georges Janssens | Keynote Speaker
Friday April 4th | 10:45-11:30 | 't Speuld

It's happening as you're reading this. It will happen during the lecture. Join to take a tour through the molecular reasons for why we age.

Workshops

Thursday April 3rd | 13:45 - 15:00

Focus

Powerpoint Karaoke
Marieke van Laar

For some people it's a recurring nightmare: you suddenly have to give a presentation without preparation. This can become your dream to come true with Powerpoint Karaoke. It is a game in which you learn how to give a convincing and interactive spontaneous presentation, using random slides. You learn to captivate and engage your audience and you will experience your own creativity and confidence. The best presentation you never prepared!

Fantasie

Sleep, light and the biological clock: How to optimize it for yourself and the relevance for your research
Marijke Gordijn

Your body runs on internal clocks, with a master clock in the suprachiasmatic nucleus of the hypothalamus. This biological clock regulates rhythms in sleep, body temperature, hormones, and performance. The most restorative sleep happens during your biological night, and physiological functions vary by time of day. Disrupting your internal clock can also cause serious health issues, known as "circadian syndrome." Understanding key Zeitgebers like light and melatonin may help us improve behavior, diagnoses, and treatments.

Daadkracht

Action painting
Ilona Boekenoogen

It is already in the name: We are going to be in action while painting! You will work with a canvas which lays on the ground, so that you'll be able to walk around it and drip paint on it. So yes, really, in this workshop you will create an abstract painting by dripping and throwing down paint. The best part is, you don't even have to be an amazing artist to create a super special painting, because your painting will reflect how much fun you had painting in action. If you want to be creative, then this will be your best painting experience yet!

Verwondering

Organizing your PhD project: Lack of time or organization?
John van Rouwendaal

The triple constraint or iron triangle of project management is formed by scope, money, and time. For many PhD students our biggest challenges are particularly around time. At a strategic level, a huge puzzle is how to take time into account when choosing between projects. At an operational level, everyone struggles to find time for projects. Join us for an interactive session where we will dissect these struggles and share strategies to take control of your PhD workload.

Levendig

How to: Presentations and public speaking
Dirk van Dorsselaer

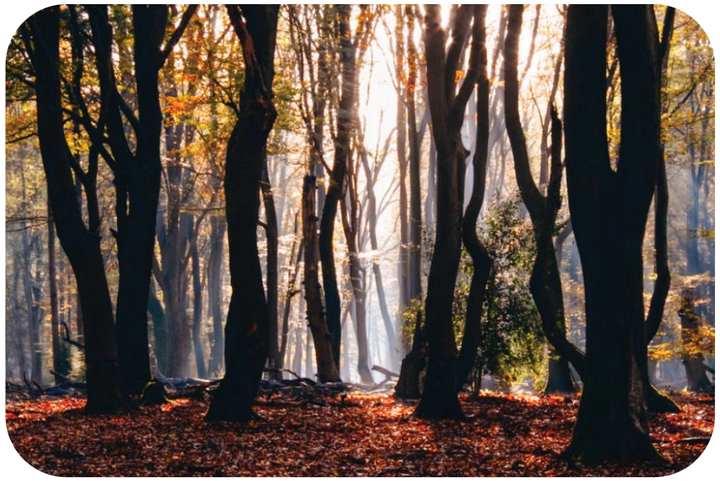
Presenting: Many people dread presenting, contrary to what many people think, you can definitely learn it. It is a matter of doing, paying attention to a few rules and above all practicing a lot. In this training we will watch a few fragments of classic speeches to learn from and then we will practice in small groups and a few volunteers will present to the entire group.

Forest Walk
Thursday April 3rd | 15:00-15:45

NOTE: This is not a guided walk.
Speulderbos (the forest around us) is a wonderful place for a walk in the nature. Take this moment to explore the routes. If you're quick enough maybe you can fit both routes in, but be quick because you don't want to miss the Out of the Box speaker!

Check out these two routes!

These flyers can be found at the hotel reception too

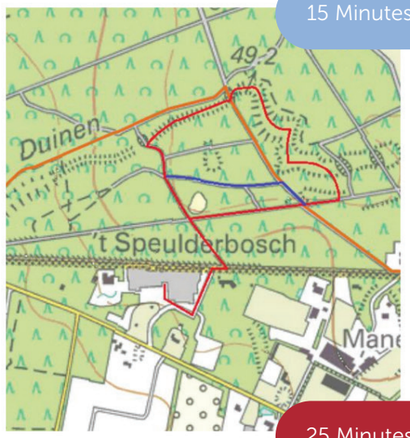


Route 1

Fun and refreshing flat walk along the edge of the forest.

1. Depart from the main entrance of the hotel. Turn left and walk around the hotel across the parking lot. At the end of the parking lot, turn right onto the sandy path and then immediately left through a small gate.
2. Continue through the forest and take the second path on the right.
3. At the end of the path, turn right.
4. You will now reach an intersection; turn right here.
5. Follow the wide forest path for approximately 220 meters until you see the fairy ring on your right. At the intersection there, turn left.
6. Go through the gate and turn right. From here, walk back through the parking lot to the main entrance of the hotel.

15 Minutes!



Route 2

A true introduction to the Speulderbos with some elevation differences.

1. Depart from the main entrance of the hotel. Turn left and walk around the hotel across the parking lot. At the end of the parking lot, turn right onto the sandy path and then immediately left through a small gate.
2. Walk straight ahead until you reach the top of the dunes.
3. At the top of the dunes, on your right, you will see an orange sign with a white arrow; follow this route as it winds through the dunes.
4. At the end of the path, the route turns left. You should turn right.
5. Follow the wide forest path for about 300 meters until you see the fairy ring on your right; at this intersection, turn left.
6. Go through the gate and turn right. From here, walk back through the parking lot to the main entrance of the hotel.

25 Minutes!

Morning activities
Friday April 4th | 07:30-08:15

Outside

Bootcamp

Feel like getting sweaty first thing in the morning? There's nothing like getting your heart rate up high outside in nature. Through good weather and bad, this is the time to push yourself before enjoying your breakfast and the rest of the itinerary.

Verwondering

Yoga

Start your morning with a fine blend of mindfulness, meditation, and strength. This yoga class will be beginner and advanced friendly, with the intention of creating a space where you can wake up your muscles and mind.

Thursday

Session A

10:15-11:00

Plenary session
‘t Speuld

Session A | ‘t Speuld

Inhibition of hepatic bile salt uptake attenuates pre-existing diet-induced metabolic dysfunction-associated steatohepatitis in mice

Claire Groenen
Amsterdam UMC, University of Amsterdam, Tytgat Institute for Liver and Intestinal Research, Amsterdam, The Netherlands

Stan van de Graaf
Amsterdam UMC, University of Amsterdam, Tytgat Institute for Liver and Intestinal Research, Amsterdam, The Netherlands

Background and objective
Metabolic dysfunction-associated steatotic liver disease (MASLD) affects over 30% of the global population and is characterized by fat accumulation in the liver. MAFLD can progress into steatohepatitis (MASH), which involves inflammation that can lead to fibrosis, and eventually cirrhosis, and liver failure. There is currently a lack of approved treatments for MASH. Bile salts are signaling molecules that modulate glucose and lipid metabolism, and inflammation. Inhibition of the Sodium-dependent Taurocholate Cotransporting Polypeptide (NTCP) increases bile salts in the blood. We investigated if inhibition of NTCP with Myrcludex B (MyrB), a safe and approved drug for treatment of hepatitis B and D, could reduce liver steatosis, inflammation and fibrosis in a MASH mouse model.

Method and results
C57BL/6J oatp1a1/1a4/1b2/ldlr-/- mice were used to mimic human hepatic bile salt dynamics. Mice received a high-fat-high-cholesterol diet and fructose water for 16 weeks to induce MASH. Subsequently, mice received subcutaneous injections of MyrB or vehicle for 6 weeks. MyrB increased plasma bile salt levels ~20-fold. MyrB decreased liver to body weight ratio and tended to reduce liver steatosis and fibrosis scores in male mice compared to vehicle. MyrB lowered plasma triglyceride levels and restored dysregulated glucose clearance and insulin levels compared to vehicle mice. MyrB lowered abundance of monocytes in plasma and liver and caused a shift towards a less inflammatory (Ly6ChighTREML4low) and more regulatory (Ly6ClowTREML4high) profile.

Conclusion/discussion
MyrB tended to reduce liver steatosis and fibrosis and reduced inflammation in a MASH mouse model. These findings suggest that MyrB may be a promising therapeutic for MASH.

Key words
MASLD, MASH, NTCP, Myrcludex B, Bile salts

Exploring the Impact of LxA4, RvD1, and RvE3 on Intestinal Inflammatory Response: Insights from a Human Intestinal Organoid Model

Jing Chen
Amsterdam UMC, University of Amsterdam, Tytgat Institute for Liver and Intestinal Research, Amsterdam, The Netherlands

Vanesa Muncan
Amsterdam UMC, University of Amsterdam, Tytgat Institute for Liver and Intestinal Research, Amsterdam, The Netherlands

Background and objective
Damage to the intestinal epithelial barrier is a hallmark of inflammatory diseases such as necrotizing enterocolitis (NEC). Specialized pro-resolving mediators (SPMs), such as Lipoxin A4, Resolvin D1, and Resolvin E3 have been shown to aid in resolving inflammation and promote mucosal healing. This study aimed to explore the effects of SPMs on intestinal inflammatory response in an early life model.

Method and results
We established 3D and 2D organoid cultures from fetal and pediatric intestines and investigated the effect of SPM cocktail on gut epithelial maturation and barrier function. Inflammatory response of gut barrier was provoked by bacterial products such as lipopolysaccharide and flagellin stimulations in combination with pro-inflammatory cytokines tumor necrosis factor alpha and interferon gamma. Under physiological conditions we observed no effect of SPMs treatments on gut epithelial maturation. Upon cytokine challenge there was no modulation of inflammatory tone of gut barrier by SPMs. However, during the repetitive wounding and recovery assay, SPM pre-treatment accelerated barrier recovery and maintained barrier integrity for 24 hours after repeated injuries.

Conclusion/discussion
Our findings suggest that SPMs have protective benefits for epithelial barrier recovery in mechanically wounded monolayers, although their ability to reverse bacterial product or cytokine-induced damage is limited. These results provide valuable insights into the therapeutic potential of SPMs in neonatal intestinal inflammation.

Key words
Specialized pro-resolving mediators;SPMs;necrotizing enterocolitis; preterm infants; epithelial barrier

Improving the diagnosis of thyroid disease by establishing multi-ethnic reference intervals for thyroid hormones, a collaboration with the HELIUS cohort

Kitty Latupeirissa
Amsterdam UMC, University of Amsterdam, Endocrine Laboratory, Amsterdam, The Netherlands

Annemieke Heijboer
Amsterdam UMC, Vrije Universiteit Amsterdam, Endocrine Laboratory, Amsterdam, The Netherlands

Background
Laboratory tests are essential in diagnosing hypo- and hyperthyroidism, as these conditions are largely defined by thyroid markers Thyroid Stimulating Hormone (TSH) and free Thyroxine (fT4) being outside reference intervals (RIs). Reliable RIs are crucial to minimize misclassification and inappropriate treatment. Previous literature have shown that ethnicity influences thyroid hormone levels in healthy people, with significant differences in TSH and fT4 concentrations among Black, White, Mexican American, and Chinese populations, highlighting the need for tailored RIs. Current RIs are largely based on Caucasian populations, leading to misclassification and poorer health outcomes for ethnic minorities. This study aims to establish ethnicity-specific RIs for thyroid hormones, improving diagnostics for minority populations.

Hypothesis
By establishing ethnicity-specific RIs for thyroid hormones, the number of misclassified patients will decrease, resulting in improved and more equitable health outcomes for thyroid diseases.

Research plan
We will collaborate with the HELIUS study, a large cohort study including people from the six leading ethnic groups in Amsterdam (Dutch, African Surinamese, South-Asian Surinamese, Ghanaian, Turkish and Moroccan). We will measure TSH and fT4 using two widely used immunoassays in 6100 HELIUS cohort blood samples from men and women of all ages and all participating ethnic groups. We will calculate the 95% reference intervals with 90% confidence intervals according to the guidelines.

Anticipated results
Our study will contribute to the advancement in thyroid disease diagnostics towards a precision medicine approach, leading to optimized treatment plans, contributing to more inclusive and effective healthcare.

Key words
Reference intervals, ethnicity, thyroid disease, diagnostics, HELIUS study

Drop-of-blood metabolomics for lifestyle efficacy and healthy aging

Maria Tretowicz
1. Laboratory Genetic Metabolic Diseases, Amsterdam UMC, University of Amsterdam, The Netherlands
2. Amsterdam Gastroenterology, Endocrinology, and Metabolism Institute, Amsterdam, The Netherlands.

Riekelt Houtkooper
1. Laboratory Genetic Metabolic Diseases, Amsterdam UMC, University of Amsterdam, The Netherlands
2. Amsterdam Gastroenterology, Endocrinology, and Metabolism Institute, Amsterdam, The Netherlands.

Background
Understanding the impact of lifestyle factors, such as exercise or supplementation, on aging is crucial for developing strategies to enhance well-being and functional capacity during aging. Traditional assessment methods often rely on invasive tests, subjective evaluations, or biomarkers, which limit insights into the complexity of human physiology and aging. These approaches are time-consuming and lack scalability, making it difficult to apply findings broadly.

Hypothesis
To address this challenge, we propose drop-of-blood metabolomics as an innovative, high-throughput tool for objectively and comprehensively assessing the biological effects of lifestyle interventions. Using liquid chromatography coupled with high-resolution mass spectrometry (LC-MS), we have optimized a method for comprehensive analysis from just a 10 µL whole-blood sample.

Research plan
With appropriate sample handling, this includes targeted analysis (e.g., NAD+ quantification), semi-targeted analysis of approximately 100 metabolites, and untargeted analysis of up to 20,000 features. Unlike traditional methods that rely on venipunctured blood or processed plasma, serum, or PBMCs, metabolomics on drop-of-blood provides an almost non-invasive approach with minimal processing while still detecting subtle metabolic changes.

Anticipated results
This method will allow for the identification of key metabolic pathways and metabolic fingerprints associated with lifestyle interventions. By leveraging this transformative technology, this study aims to uncover biological signatures of lifestyle interventions, offering deeper insights into their role in promoting healthy aging across diverse cohorts.

Key words
Whole-blood, drop-of-blood, metabolomics, interventions, healthy aging

Discovery of lncRNA-dependencies in hepatocellular carcinoma using a GENCODE-based Rfx-Cas13D screening approach

Steven Eleonora
Laboratory of Experimental Oncology and Radiobiology, Cancer Center Amsterdam, Amsterdam UMC and University of Amsterdam, Amsterdam, the Netherlands.

Nicolas Léveillé
Laboratory of Experimental Oncology and Radiobiology, Cancer Center Amsterdam, Amsterdam UMC and University of Amsterdam, Amsterdam, the Netherlands.

Background
Hepatocellular carcinoma (HCC) is the most common and aggressive form of liver cancer in which the majority of patients are diagnosed an advanced stage when the tumor is unresectable. First line treatment for these HCC patients consist of Sorafenib, Lenvatinib (multikinase inhibitors) or a combination of atezolizumab (a-PDL1) and bevacizumab (a-VEGF). Both these therapies however show limited benefit for HCC patients; mainly due to the occurrence of therapy resistance. For this reason we are in need of novel tumor-specific targeted therapeutic approaches.

Hypothesis
Both the genetic landscape and proteome of HCC have thoroughly been studied. However, the functional role that the non-coding RNA landscape plays in the disease has not been studied to the same extent. Long non-coding RNAs (lncRNAs), a group of RNA molecules that do not have a protein-coding potential, but play important roles in cellular processes and often have highly tissue- and tumor specific expression patterns. This makes these molecules ideal candidates for novel therapeutics.

Research plan
For this reason we designed a CRISPR Rfx-Cas13D library targeting all annotated long non-coding RNAs in the GENCODE database. Using this library we will identify lncRNAs with an essential function in the proliferation of HCC cells, study their mechanism of action using functional assays and test their therapeutic potential by targeting them using an siRNA approach in vivo. Through identifying the involvement of non-coding RNAs in the oncogenic signaling in HCC, we will discover novel vulnerabilities that can be used to improve the treatment of unresectable HCC patients.

Anticipated results
Discovery of lncRNA-dependencies in hepatocellular carcinoma using a GENCODE-based Rfx-Cas13D screening approach

Keywords
lncRNA CRISPR screening hepatocellular carcinoma

Session B

12:15-13:00

Parralel sessions

Session B1 | Verwondering

Diederick van Doorn	Correlation between transient elastography, clinical scores and liver histology in patients with metabolic dysfunction-associated steatotic liver disease
Milou van Driel	Targeting Wnt Signalling by Vaccination for Prevention of CRC
Thirza van Croonenburg	Quantitative MRI for predicting early treatment response in perianal Crohn's disease
Tim van der Plas	Determinants of Peritoneal Metastasis
Jutta van Crevel	Incorporating the Enhanced Liver Fibrosis (ELF) test to improve the predictive value of the Amsterdam-Oxford prognostic model in patients with PSC

Session B2 | Levendig

Anne-Sophie Stroes	ALT is an effective screening tool for advanced MASLD in children with obesity and overweight
Wei Jiang	Neuropathological change in the nucleus basalis of Meynert in people with type 1 or type 2 diabetes
Reimer Janssen	Evaluating the correlation between MRI and transperineal ultrasound findings in patients with perianal fistulizing Crohn's Disease: a pilot study
Merel Goedkoop	The metabolic effects of the menopause on the liver
Tianqi Mu	Unraveling the correlation between Candida albicans induced epithelial barrier disturbance and abdominal pain in quiescent IBD

Session B3 | Fantasie

Amber Meurs	Genome-engineered hepatic cells to provide novel insights into the spatiotemporal metabolism of APOB and APOB-containing lipoprotein secretion
Job Kesselaar	YM155 as effective treatment for colorectal peritoneal metastases by inhibiting the mitochondrial function.
Lana Verstoep	Therapeutic drug monitoring and prediction of clinical outcome in paediatric and adolescent patients with Crohn' disease treated with methotrexate (MTX): taking an established drug a step further towards personalized treatment.
Ke Liu	Longitudinal Single-Cell Multi-Omic Analysis to Characterize Treatment Response Dynamics in Crohn's Disease
Junhuan Mou	Role of fermentation by intestinal yeast in abdominal pain during quiescent (qIBD).

Session B4 | Focus

Evert Manders	Repurposing biosimilars, rethinking costs: A framework for sustainable drug pricing for repurposed bevacizumab for intravitreal injections
Anne Petersen	FUNCTIONAL B12 DEFICIENCY YEARS AFTER ILEAL RESECTION IN INFANCY: THE NEED FOR LONG-TERM MONITORING
Ayano Shiba	Voluntary running and estrous cycle modulate ?FOSB in the suprachiasmatic nucleus of the Wistar rat

Correlation between transient elastography, clinical scores and liver histology in patients with metabolic dysfunction-associated steatotic liver disease

Diederick van Doorn
Amsterdam UMC, Universiteit van Amsterdam, Gastroenterology and Hepatology, Amsterdam, The Netherlands

Bart Takkenberg
Amsterdam UMC, Universiteit van Amsterdam, Gastroenterology and Hepatology, Amsterdam, The Netherlands

Background and objective
Metabolic dysfunction-associated steatotic liver disease (MASLD) is a rising cause of chronic liver disease. Liver stiffness measurement (LSM) is widely used as diagnostic tool, but its accuracy is uncertain. The aim of this study was to assess the correlation between LSM and liver histology in MASLD.

Methods and results
We conducted a retrospective cohort study in patients with biopsy confirmed MASLD who underwent LSM within 6 months before biopsy. The primary endpoint was the correlation between LSM and histological grade of fibrosis. Secondary endpoints were correlation between Controlled Attenuation Parameter (CAP) values and histological grade of steatosis, and to validate LSM cut-off values.

We included 139 patients. Histological distribution of fibrosis stages was as follows: F0: 5%, F1: 15%, F2: 56%, F3: 14%, and F4: 9%, with a median LSM (IQR) of 8.9 (20.4), 7.8 (4.5), 8.8 (5.4), 12.8 (4.8), and 37.4 (43.1) kPa, respectively. We found a positive correlation between LSM and histological fibrosis grade ($r = .42$, $p<0.001$). LSM = 12 kPa demonstrated an excellent sensitivity (0.75) and specificity (0.80) in detecting severe fibrosis (=F3), with an area under the receiver operating characteristics (AUROC) curve of 0.80. We found no significant differences in CAP between each grade of steatosis.

Conclusion / discussion
LSM cannot discriminate between low levels of fibrosis but can accurately identify severe fibrosis/cirrhosis in MASLD patients using a threshold of LSM = 12 kPa. LSM in combination with non-invasive scores may be suitable to confirm severe fibrosis or aid in the decision making for the need of liver biopsy.

Keywords
MASLD, Fibrosis, Steatosis, Non-invasive tests, Diagnostics

Targeting Wnt Signalling by Vaccination for Prevention of CRC

Milou S. van Driel
Laboratory of Experimental Oncology and Radiobiology, Oncode Institute, Cancer Center Amsterdam, Amsterdam UMC and University of Amsterdam, Amsterdam, The Netherlands.

Louis Vermeulen
Laboratory of Experimental Oncology and Radiobiology, Oncode Institute, Cancer Center Amsterdam, Amsterdam UMC and University of Amsterdam, Amsterdam, The Netherlands.

Background and objective
Colorectal cancer (CRC) development is driven by the progressive accumulation of mutations in cancer driver genes such as adenomatous polyposis coli (APC). APC mutations are considered early events that lead to hyperactivation of the Wnt/ß-catenin pathway and facilitate the development of premalignant adenomas in the intestine. We have recently revealed that, within the intestinal crypt, Apc-mutant cells act as 'supercompetitors' that actively disadvantage normal intestinal stem cells (ISCs). Mechanistically, Apc-mutants secrete a set of Wnt antagonists such as NOTUM, WIF1, and DKK2 that force normal ISCs into differentiation. Moreover, we have demonstrated that modulating cell competition in favour of normal ISCs prevents the development of intestinal adenomas and can offer a promising strategy to prevent CRC initiation.

Methods and results
In this study, we evaluate the preventive potential of cancer vaccines in an in vivo mouse model of Apc-driven tumorigenesis. Using the immune-Boost (iBoost) vaccine technology, that ensures the protein from the tumour to appear foreign to the immune system, we have successfully induced an antibody response against Apc-mutant specific secreted factors NOTUM and TIMP1.

Conclusion / discussion
Our preliminary findings indicate a reduction in adenoma development following vaccination, highlighting the potential of vaccines as novel cancer prevention strategies for CRC.

Keywords
Colorectal Cancer, Cancer Vaccines, Intestinal Stem Cells, Stem Cell Dynamics

Quantitative MRI for predicting early treatment response in perianal Crohn's disease

Thirza van Croonenburg
Amsterdam UMC, Universiteit van Amsterdam, Radiology and Nuclear Medicine, Amsterdam, the Netherlands

Jaap Stoker
Amsterdam UMC, Universiteit van Amsterdam, Radiology and Nuclear Medicine, Amsterdam, the Netherlands

Background
MRI with conventional sequences is the recommended imaging modality for diagnosis, classification and treatment monitoring of perianal fistulizing Crohn's disease (pfCD). However, radiological changes tend to be relatively slow.
Advanced quantitative MRI measures pathophysiology non-invasively in inflammatory disorders. DCE images capture tissue response to blood inflow over time during contrast agent delivery. IVIM-DWI assesses diffusion and perfusion affected by inflammation and fibrosis. T2* mapping reflects tissue microstructure via susceptibility differences and magnetic field heterogeneities.

Hypothesis
Microstructural changes identifiable with quantitative MRI sequences precede macroscopic radiological changes in patients treated for pfCD.

Research plan
Patients with complex pfCD, who will start with anti-TNF therapy or HBOT or MSC therapy will be included. We aim to include 25 patients per treatment. Our primary aim is to assess the utility of different advanced MRI parameters (at week 26) in predicting fistula healing at week 52.
All patients will undergo conventional and advanced MRI sequences (DCE, IVIM and T2* mapping) at baseline, week 9 and week 26. Furthermore, at week 52 all patients will undergo their conventional MRI scan.

Anticipated results
We anticipate to see change in quantitative MRI parameters at an earlier timepoint than can be seen on conventional MRI. This could possibly provide biomarkers for early prediction (week 9 or 26) of treatment response in pfCD. The early prediction of treatment response in the pfCD patient population will have a beneficiary impact on clinical decision making, by giving the ability to determine at an early stage who is likely to non-respond or respond.

Keywords
Crohn's disease | Perianal fistula | Advanced MRI | Treatment response

Determinants of Peritoneal Metastasis

Tim van der Plas
Laboratory of Experimental Oncology and Radiobiology, Cancer Center Amsterdam, Oncode Institute, Amsterdam UMC and University of Amsterdam

Maarten Bijlsma
Laboratory of Experimental Oncology and Radiobiology, Cancer Center Amsterdam, Amsterdam UMC and University of Amsterdam

Background
Peritoneal metastases (PM) are a common form of tumor cell dissemination in gastrointestinal malignancies. Although likely still underreported, an increased PM incidence has been reported over the years due to improved diagnostic techniques and registration, increased awareness, and longer survival after primary tumor diagnosis. Peritoneal metastatic disease (PMD) is associated with severe morbidity and resistance to current therapies. Given the direct dissemination route and unique microenvironment of the peritoneal cavity, specific tumor cell characteristics are required for development of PMD. Previous studies suggest that distinct histopathological, genomic, and transcriptomic features of primary gastrointestinal tumors are associated with PMD. We propose to further investigate these features, and discover drivers of PMD within and across primary cancer types.

Hypothesis
Previous studies and work in our lab show associations between certain cancer subtypes and PMD. By using cell lines from these subtypes in our in vivo peritoneal metastasis model, we expect to elucidate programs that drive PMD. In this model, subclones that are able to proliferate in the peritoneal cavity will grow out into metastases, while cell populations that don't have the capacity to survive will disappear.

Research plan
Serial re-grafting of cell lines derived from peritoneal lesions will repeatedly select for subclones that are proficient in seeding in the peritoneal cavity. The resulting cell lines will be analysed for histopathological, genomic, and transcriptomic features that drive the hyper efficient seeding.
Anticipated results
We expect to show the suggested association of certain cancer subtypes with PMD, and identify genes within and across cancer types that drive peritoneal metastasis.

Keywords
peritoneal metastasis, colorectal cancer, metastasis, transcriptomics

Incorporating the Enhanced Liver Fibrosis (ELF) test to improve the predictive value of the Amsterdam-Oxford prognostic model in patients with PSC

Jutta van Crevel
Amsterdam UMC, Universiteit van Amsterdam, Gastroenterology & Hepatology, Amsterdam, The Netherlands

Cyriel Ponsioen
Amsterdam UMC, Universiteit van Amsterdam, Gastroenterology & Hepatology, Amsterdam, The Netherlands

Background
Primary sclerosing cholangitis (PSC) is a chronic, variably progressive, cholestatic liver disease causing biliary fibrosis and cirrhosis. Multiple therapies have been studied in PSC, but none has demonstrated efficacy in halting disease progression. Another challenge concerns reliable estimation of prognosis in PSC, mainly because of the heterogeneity in clinical course progression and the variety of outcomes ranging from end-stage liver disease to development of hepatobiliary and colorectal malignancies. The Amsterdam-Oxford model (AOM), developed in 2017, predicts PSC-related outcomes with a C-statistic of 0.68, and satisfactory calibration. Although validated, further refinement is needed to achieve higher predictive accuracy. The Enhanced Liver Fibrosis (ELF) test, a serum-based measure combining biomarkers, has demonstrated good prognostic utility in PSC for detecting advanced fibrosis and predicting outcomes.

Hypothesis
Incorporating the ELF test into the AOM will improve its predictive performance, aiding clinical decision-making and personalized patient management.

Research plan
This study will be conducted using the EpiPSC2-registry, a longstanding retrospective and prospective cohort of Dutch PSC-patients. We will use previously banked samples and formally biobanked serum to determine ELF at different time points. Clinical information regarding demographic data, diagnosis of PSC, comorbidities, medication use and laboratory parameters necessary for determination of the Amsterdam-Oxford score will be collected. Follow-up data regarding complications such as liver transplantation, death, hepatobiliary malignancies and signs of liver decompensation, will be collected.

Anticipated results
We expect the modified AOM to outperform the original model in predictive accuracy and discriminatory performance. Improved prognosis estimation could optimize timing for diagnostic and therapeutic interventions, ultimately benefiting PSC patient care.

Keywords
Primary Sclerosing Cholangitis (PSC), Enhanced Liver Fibrosis (ELF), Amsterdam-Oxford model, predictive performance, prognostic refinement

ALT is an effective screening tool for advanced MASLD in children with obesity and overweight

Anne-Sophie Stroes
Amsterdam UMC, Universiteit van Amsterdam, Gastroenterology & Hepatology, Amsterdam, The Netherlands

Bart Koot
Amsterdam UMC, Universiteit van Amsterdam, Gastroenterology & Hepatology, Amsterdam, The Netherlands Amsterdam UMC

Background and objective
Metabolic dysfunction-associated steatotic liver disease (MASLD) has high prevalence among children with obesity. However, screening remains controversial as the optimal method has not been established. This study aims to evaluate the effectiveness of an Alanine Aminotransferase (ALT)-based screening algorithm for advanced MASLD in children with obesity/overweight.

Methods and results
Children 8-18 years with (i) obesity or (ii) overweight and ≥1 additional risk factor seen at obesity outpatient clinics for co-morbidity screening were included. Participants were screened for MASLD using ALT and analysed in based on ALT levels. Vibration-controlled transient elastography (VCTE) was performed to determine probable significant fibrosis (VCTE ≥7.4 kPa). Patients features associated with VCTE ≥7.4 kPa were assessed using logistic regression analysis. Diagnostic accuracy of ALT was compared to other non-invasive tests.
Among 322 children (64% male, median age 13 years, mean BMI z-score 3.5), the prevalence of VCTE ≥7.4 kPa increased significantly with ALT elevation: 1.9% for normal ALT, 16.4% for mild ALT elevation (≥ULN: ♀22 IU/L, ♀26 IU/L), 21.3% for moderate elevation (≥2ULN: ♀44 IU/L, ♀52 IU/L), and 38.9% for strong elevation (≥80 IU/L) (p<0.001). Other non-invasive tests did outperform ALT in this cohort. VCTE ≥7.4 kPa was positively associated with ALT ≥80 IU/L (OR 2.91, 95%CI: 1.25-6.74), age (OR 1.50, 95%CI 1.27-1.76), male gender (OR 2.37, 95%CI 1.04-5.40), BMI z-score (OR 3.01, 95%CI 1.62-5.61), and HOMA (OR 1.10, 95%CI 1.00-1.13).

Conclusion / discussion
This study shows that ALT is an effective primary screening tool for advanced MASLD in children with obesity or overweight.

Keywords
Paediatric, Liver fibrosis, Screening, Elastography, Prevalence

Neuropathological change in the nucleus basalis of Meynert in people with type 1 or type 2 diabetes

Wei Jiang
Amsterdam UMC, Endocrinology and Metabolism, Amsterdam, The Netherlands

Chun-Xia Yi
Amsterdam UMC, Endocrinology and Metabolism, Amsterdam, The Netherlands

Background and objective
People with type 1 or type 2 diabetes mellitus (T1DM or T2DM) often experience cognitive impaiment. We profiled cells in the nucleus basalis of Meynert (NBM) in postmortem human brain tissues to investigate neuropathological changes.

Methods and results
71 postmortem NBM samples were grouped by T1DM,T2DM and non-diabetc controls, with Braak stage 0-2 or 3-6. T1DM subjects had only Braak stage 0-2 and were thus compared only to controls with a similar Braak stage and not subjects with Braak stage 3-6. We analysed neurons expressing choline acetyluansterase (ChAT),phosphorylated-Tau, glial cells and vasculature with respective
markers. We found significantly less neuronal expression of ChAT in T1DM compared to controls and T2DM with Braak stage 0-2 Later stage hyperphosphorylated-Tau levels were higher in T2DM compared to controls with Braak stages 3-5.

Conclusion / discussion
Our results suggest that reduced acetylcholine production by NBM neurons might underlie the cognitve complains of people with T1DM. In contrast, T2DM may ex acerbate neuropathological changes associated with Alzheimer's disease-like alterations.

Keywords
Acetylcholine,Alzheimer's disease,hypoglycemia, hyperglycemia, glymphatic system, nucleus basalis of Meynert

Evaluating the correlation between MRI and transperineal ultrasound findings in patients with perianal fistulizing Crohn's Disease: a pilot study

Reimer Janssen
Amsterdam UMC, Vrije Universiteit Amsterdam, Gastroenterology and Hepatology, Amsterdam, the Netherlands

K.B. Gecse
Amsterdam UMC, Vrije Universiteit Amsterdam, Gastroenterology and Hepatology, Amsterdam, the Netherlands

Background
Perianal fistulizing Crohn's Disease (pfCD) is a severe complication of Crohn's Disease that imposes a significant healthcare burden. Accurate diagnosis and monitoring of pfCD require advanced imaging techniques. While MRI is the gold standard for detecting fistula tracts and abscesses, it is costly, time-intensive, and not universally accessible. Transperineal ultrasound (TPUS) offers a cost-effective, patient-centered alternative that could complement MRI. However, its diagnostic performance in pfCD remains underexplored.

Hypothesis
TPUS findings correlate strongly with MRI findings in patients with pfCD, demonstrating feasibility as a complementary diagnostic tool for routine clinical care.

Research plan
We propose a pilot study involving 8–10 adult patients with established pfCD scheduled for routine pelvic MRI. Patients will undergo TPUS within seven days before or after MRI. Data collection will include imaging findings (MRI: MAGNIFI-CD score; TPUS: fistula activity, abscesses, and complications) and clinical data (demographics, medical history, PDAI score). Imaging features will be compared using descriptive statistics, and diagnostic agreement will be assessed using Cohen's kappa coefficient. If feasibility is confirmed, the study will be expanded to a cohort of 15–20 patients.

Anticipated results
We anticipate TPUS will demonstrate high agreement with MRI in detecting fistula tracts and abscesses. The study will provide critical data on TPUS feasibility, sensitivity, and specificity, supporting its integration into routine care. This project aims to improve diagnostic accessibility and outcomes for patients with pfCD, aligning with the goals of advanced diagnostics.

Keywords
IBD; intestinal ultrasound; imaging; monitoring; clinical

The metabolic effects of the menopause on the liver

Merel Goedkoop
Amsterdam UMC, Universteit van Amsterdam, Endocrinology laboratory, Amsterdam, The Netherlands

Anita Boelen
Amsterdam UMC, Universteit van Amsterdam, Endocrinology laboratory, Amsterdam, The Netherlands

Background
The menopause is the permanent loss of menstrual cycles. The menopause is caused by a shift in hormones caused by aging of the follicles. The drop in hormones results in changes throughout the body, such as increased insulin sensitivity and visceral adiposity in the liver. Increasing the risk for Metabolic dysfunction-Associated Steatotic Liver Disease (MASLD). Until date there is not a reliable liver cell model to study the effects of the menopause and hormonal changes on liver metabolism.
Hypothesis
Therefore, in this project the focus will be on setting up a reliable liver cell model for women during or after the menopause.

Research plan
In order to do this, the idea is to characterize the immortal cell lines HepG2, HepaRG, Huh7 and two primary cell lines. We will check the cell lines on the presence of receptors for important hormones during the menopause. After characterization, we will add pre- and post-menopausal hormone mixes and look at the effects on steatoses and inflammation.

Anticipated results
We expect to see more steatoses and inflammation in our post-menopause culture than in the pre-menopause culture. Altogether, this can hopefully result in a reliable liver model of menopausal women and contribute to more reliable therapy testing for these women.

Keywords
Menopause, liver, cell culture, MASLD, endocrinology

Unraveling the correlation between Candida albicans induced epithelial barrier disturbance and abdominal pain in quiescent IBD

Tianqi Mu
Amsterdam UMC, University of Amsterdam, Tytgat Institute for Liver and Intestinal Research, Amsterdam, The Netherlands

Wouter de Jonge, Rene van den Wijngaard
Amsterdam UMC, University of Amsterdam, Tytgat Institute for Liver and Intestinal Research, Amsterdam, The Netherlands

Background and objective
Abdominal pain is prevalent in quiescent IBD (qIBD-pain˜40%) and associates with increased paracellular permeability of colon. C. albicans is a commensal opportunistic fungus that can switch from yeast to hyphae and damage intestinal barrier. We hypothesized that qIBD-pain C. albicans fecal isolates are more detrimental to barrier function than qIBD-no-pain isolates.

Methods and results
We obtained 17 qIBD-pain and 12 qIBD-no-pain isolates. Transepithelial electrical resistance (TEER) of Caco-2 Bbe monolayer/live C. albicans co-cultures was continuously monitored by CellZscope for 72hours. Fluorescent probes (9Å and 46Å) were added apically at 72h and basolateral levels were assessed 120 minutes later. Concanavalin A and anti-Candida antibody stainings were used to distinguish intra and extracellular presence of C. albicans hyphae in Caco-2 Bbe cells.
C. albicans isolates decreased TEER to different degrees, but due to large spread, there was no significant difference between groups. Isolates showing fast decease in TEER (”high damage isolates”) showed increased paracellular permeability to 9Å and 46Å. Intermediate and low damage isolates showed passage of 9Å only. Stainings indicated that hyphal invasion in Caco-2 was only high when the drop in TEER was fast and low or absent in others. Prior to decrease, all isolates showed temporarily increased TEER which was significantly higher in qIBD-no-pain isolates.

Conclusion / discussion
The level of barrier damage inflicted by C. albicans was isolate dependent and not different between groups. Importantly, we observed a temporary increase in TEER which was significantly higher in the no-pain group. Mechanism and relevance hereof are yet to be addressed.

Keywords
C. albicans, IBD, abdominal pain, intestinal barrier function, hyphae

Genome-engineered hepatic cells to provide novel insights into the spatiotemporal metabolism of APOB and APOB-containing lipoprotein secretion

Amber Meurs
Amsterdam UMC, AMC, Department of Medical Biochemistry, University of Amsterdam, Amsterdam, the Netherlands

Noam Zelcer
Amsterdam UMC, AMC, Department of Medical Biochemistry, University of Amsterdam, Amsterdam, the Netherlands

Background and objective
APOB-containing very-low-density lipoprotein (VLDL) production and secretion by hepatocytes is a central determinant of hepatic and circulating lipid levels. Impairment of these processes is associated with the development of multiple diseases. Despite the discovery of genes that govern hepatic VLDL metabolism, our understanding of the different mechanistic steps involved is incomplete. An impediment to these studies is the lack of tractable hepatocyte-based systems to study intracellular APOB.

Methods and results
To facilitate the cellular study of VLDL metabolism, we generated human hepatic cell lines in which CRISPR/Cas9-based genome-engineering was used to introduce the fluorescent protein mNeon into the APOB gene. We extensively tested the functionality of this model and used HepG2-APOBmNeon cells to discover the E3 ligase responsible for the degradation of APOB. In addition, we used these cells to perform a whole-genome screen to identify new determinants of intracellular APOB expression.
The genome-engineering of the hepatocytes results in the production of APOB-mNeon that localizes predominantly to the ER and Golgi, as imaged using immunofluorescence. The production and secretion of APOB-mNeon can be quantitatively followed in medium over time, and results in production of lipoproteins that can be internalized. This production and secretion are sensitive to established treatments and genetic modifiers known to influence VLDL production. The E3-ligase screen led to the identification of SYNV1 as the E3 responsible for degradation of APOB. Furthermore, we identified genes that influence APOB expression and are not related to APOB yet.
Conclusion / discussion
In conclusion, the reported cells allow the study of hepatic VLDL assembly and secretion.

Keywords
APOB, VLDL, CRISPR-Cas9, Cell model, Fluorescence

YM155 as effective treatment for colorectal peritoneal metastases by inhibiting the mitochondrial function

Job Kesselaar
1 Laboratory of Experimental Oncology and Radiobiology, Cancer Center Amsterdam, Amsterdam UMC and University of Amsterdam, Amsterdam, The Netherlands
2 Amsterdam Gastroenterology Endocrinology Metabolism, Amsterdam, The Netherlands
3 Oncode Institute, Jaarbeursplein 6, 3521 AL Utrecht, The Netherlands.
4 Cancer Center Amsterdam, Cancer Biology, Amsterdam, the Netherlands

Louis Vermeulen
1 Laboratory of Experimental Oncology and Radiobiology, Cancer Center Amsterdam, Amsterdam UMC and University of Amsterdam, Amsterdam, The Netherlands
2 Amsterdam Gastroenterology Endocrinology Metabolism, Amsterdam, The Netherlands
3 Oncode Institute, Jaarbeursplein 6, 3521 AL Utrecht, The Netherlands.
4 Cancer Center Amsterdam, Cancer Biology, Amsterdam, the Netherlands

Background and objective
Peritoneal metastases (PM) derived from CRC are associated with a poor prognosis. Current treatment in the resectable setting is a combination of cytoreductive surgery and HIPEC. Although the combination of the two has curative potential, this is mainly due to the cytoreductive surgery, as chemotherapy is relatively ineffective against PM. Therefore, new drugs with high efficacy against PM could improve outcomes.

Methods and results
We previously found that the mesenchymal CMS4 of CRC strongly associates with the ability to metastasize to the peritoneum.
By correlating the CMS4 probability score and the relative efficacy of drugs annotated in the PRISM database, we discovered YM155 as a potential candidate for treating PM.
To replicate HIPEC, cell lines and PM-derived organoids were briefly exposed to YM155, followed by cell viability and outgrowth assays respectively, validating YM155's efficacy in vitro.
In an in vivo model for PM, three doses of intraperitoneal YM155 completely inhibited tumor growth. Moreover, in a survival study of 12 weeks, all treated mice were still alive at the experiment's endpoint. To explain YM155's rapid action, we examined the previously described apoptosis mechanism. However, rescue experiments and KDs of YM155's target indicated it does not follow this mechanism. Instead, Seahorse flux analysis and metabolomics experiments revealed YM155 targets mitochondria within minutes.

Conclusion / discussion
Overall, the combination of the in vitro and in vivo data indicates that YM155 is an improvement on the current treatment of PM in a HIPEC setting or through IP administration.

Keywords
CRC, Peritoneal metastases, YM155, Mitochondria

Therapeutic drug monitoring and prediction of clinical outcome in paediatric and adolescent patients with Crohn' disease treated with methotrexate (MTX): taking an established drug a step further towards personalized treatment.

Lana Verstoep
Amsterdam UMC, Universiteit van Amsterdam, Pediatric Gastroenterology, Amsterdam, The Netherlands

Tim de Meij
Amsterdam UMC, Vrije Universiteit Amsterdam, Pediatric Gastroenterology, Amsterdam, The Netherlands

Background
The updated ECCO/ESPGHAN guidelines position MTX as a first-choice immunomodulator for remission maintenance or after thiopurine failure/intolerance, and as concomitant treatment with TNFa-inhibitors. These guidelines reflect the growing use of MTX in paediatric Crohn's disease (CD), due to its efficacy, affordability and safety. In contrast, thiopurines raise concerns due to the risk of malignancies and hemophagocytic lymphohistiocytosis (HLH). Therefore, MTX is an attractive option as it is safe, inexpensive, and effective.

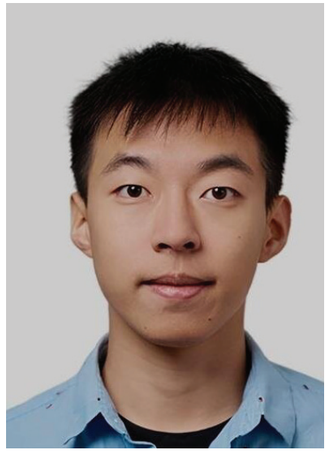
Hypothesis
We hypothesize that higher levels of MTX polyglutamates (MTX-PG) are associated with a clinical response to MTX monotherapy as well as combination therapy with infliximab and MTX. We expect MTX-PG to be a valuable therapeutic drug monitoring (TDM) tool improving clinical outcomes.

Research plan
Multicentre prospective longitudinal cohort study of paediatric and adolescent CD patients (4-28y) starting MTX and infliximab + MTX maintenance treatment. Patients will be followed-up for 1 year. Clinical data including disease activity scores, blood samples and faeces will be collected at different time points. Intracellular MTX-PGs, genetic and metabolic factors in the MTC pathway as well as the faecal microbiome and metabolome of treated patients will be measured.

Anticipated results
We will determine MTX-PG accumulation patterns over time and identify baseline determinants influencing accumulation patterns of MTX-PG. We will establish the relationship and effect between MTX-PG's on clinical response/drug survival/adherence and toxicity. All together we expect MTX-PG's to be a valuable TDM tool for targeted MTX use. Finally, a prediction model and clinical decision-making tool will be constructed by identifying predictors of clinical efficacy before MTX start.

Keywords
Methotrexate, MTX-PG, Crohn's disease, Therapeutic drug monitoring

Longitudinal Single-Cell Multi-Omic Analysis to Characterize Treatment Response Dynamics in Crohn's Disease



Ke Liu
Amsterdam UMC, University of Amsterdam, Tytgat Institute for Liver and Intestinal Research, Amsterdam, The Netherlands

Andrew Li Yim
Amsterdam UMC, University of Amsterdam, Tytgat Institute for Liver and Intestinal Research, Amsterdam, The Netherlands

Background
Crohn's disease (CD) is a chronic inflammatory bowel disease within the gastrointestinal tract. Therapies that target specific mediators of inflammation include vedolizumab, ustekinumab, and tofacitinib, there is a significant heterogeneity in patient responses to therapeutic interventions, underscoring the need for precision medicine guided by reliable biomarkers.

Hypothesis
Previous studies, including the EPIC-CD cohort study, have demonstrated the potential of transcriptomic and epigenomic data from blood in identifying predictors associated with treatment response to ustekinumab, vedolizumab, and tofacitinib. However, as the data was obtained from heterogeneous tissue, the underlying mechanisms distinguishing non-responders from responders remain poorly understood. Recent technological advances in single-cell research provide unprecedented insights into cellular functions. Single-cell multi-omics approaches, such as smartRRBS, allow for the simultaneous profiling of genetic activity and cellular modifications within individual cells, offering a more comprehensive view of cellular communication.

Research plan
The aim of my PhD is to utilize advanced single-cell multi-omics technologies to simultaneously profile the transcriptome and DNA methylome of both peripheral blood and intestinal biopsies samples from CD patients. We plan to conduct smartRRBS on patients samples at baseline and after treatment, enabling a longitudinal analysis.

Anticipated results
By integrating transcriptomic and epigenomic data at the single-cell level across multiple time points, we seek to identify cell type specific biomarkers associated with treatment response, develop a predictive model for treatment response, and uncover the molecular mechanisms underlying therapeutic outcomes. The insights gained from this research could ultimately guide the development of more effective, personalized treatment strategies for CD patients.

Keywords
single-cell muli-omics, Crohn's Disease, biomarkers, treatment response, longitudinal analysis

Role of fermentation by intestinal yeast in abdominal pain during quiescent (qIBD).

Junhuan Mou
Amsterdam UMC, University of Amsterdam, Tytgat Institute for Liver and Intestinal Research, Amsterdam, The NetherlandsThe Netherlands

Wouter de Jonge
Amsterdam UMC, University of Amsterdam, Tytgat Institute for Liver and Intestinal Research, Amsterdam, The NetherlandsThe Netherlands

Background and objective
It has been shown that production of gas, due to carbohydrate fermentation by gut microbiota, and subsequent colonic distension contributes to abdominal pain. Earlier, we showed that gut fungi (i.e. the mycobiome) may contribute to abdominal pain and recently observed, in vitro, that the fecal mycobiome contributes to fermentation. Thus we hypothesize that intestinal yeast may contribute to abdominal pain by gas production.

Methods and results
Methods: We isolated C. albicans from fecal samples of 12 qIBD (no pain), and 17 qIBD-pain patients. Using the Gaspro system we measured cumulative gas production for 48 hours while culturing C. albicans in medium containing fructose.
Results: Fermentation kinetics varied between isolates. However, due to a large spread in each group, differences between groups were not significant.

Conclusion / discussion
Although C. albicans may contribute to intestinal gas production, the current data do not show differences between pain and no-pain groups.

Keywords
IBD, abdominal pain, intestinal fungi, fermentation.

Repurposing biosimilars, rethinking costs: A framework for sustainable drug pricing for repurposed bevacizumab for intravitreal injections

Evert Manders
Medicine for Society, Platform at Amsterdam University Medical Center, Amsterdam, The Netherlands

Saco de Visser
1. Medicine for Society, Platform at Amsterdam University Medical Center, Amsterdam, The Netherlands
2. Centre for Future Affordable & Sustainable Therapy development (FAST), The Hague, The Netherlands

Background and objective
Bevacizumab, originally developed by Genentech under the brand name Avastin® as an anti-cancer drug, has gained widespread off-label use in ophthalmology due to its similar mechanism of action to other anti-VEGF treatments and its significantly lower cost compared to available on label alternatives for ophthalmological indications. While off-label bevacizumab has been standard in clinical practice for over a decade, recently, a repurposed formulation (brand name: Lytenava®, Outlook Therapeutics Ltd), specifically for vascular retinal conditions, received marketing approval from the European Medicines Agency. This raises questions about what the price for a repurposed formulation should reasonably be, reflecting the efforts to obtain regulatory approval. This study examines potential cost-based-plus pricing for such a repurposed formulation of bevacizumab.

Method and results
By evaluating the pricing structure using a novel pricing framework across four scenarios and through an analysis of critical cost components—including, among others, research and development expenditures, manufacturing costs, and capital costs—the study proposes a price range of €44 to €72 per injection.

Conclusion/discussion
The explicit breakdown of these cost components provides valuable insights into the economic structure of repurposed biosimilars like bevacizumab, emphasizing how a cost-based-plus pricing model can support more transparent and informed negotiations between pharmaceutical companies and healthcare payers. Ultimately, this approach contributes to the development of pricing strategies that balance affordability for healthcare systems with sustainable returns for manufacturers while fostering the broader development of repurposed treatments.

Key words
Drug repurposing, bevacizumab, neovascular age-related macular degeneration, retinal vein occlusion, diabetic macular oedema

Functional B12 deficiency years after ileal resection in infancy: the need for long-term monitoring

Anne Petersen
1. Department of Pediatric Surgery, Emma Children's Hospital, Amsterdam UMC, location University of Amsterdam, Meibergdreef 9, Amsterdam, the Netherlands. 2. Amsterdam Gastroenterology Endocrinology Metabolism Research Institute, 1105 AZ Amsterdam, The Netherlands.

Merit Tabbers
1. Amsterdam Gastroenterology Endocrinology Metabolism Research Institute, 1105 AZ Amsterdam, The Netherlands. 2. Amsterdam Reproduction & Development Research Institute, 1105 AZ Amsterdam, The Netherlands. 3. Department of Pediatric Gastroenterology and Nutrition, Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, The Netherlands.

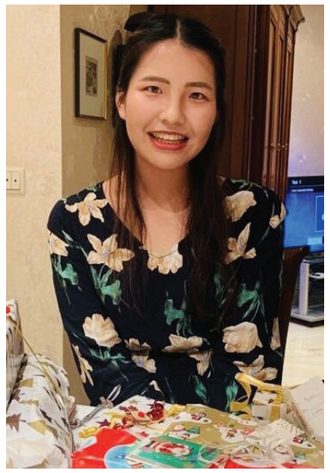
Background and objective
Ileal resection in infancy, sometimes required for life-threatening conditions, may impair vitamin B12 absorption. Vitamin B12 deficiency, characterized by elevated methylmalonic acid (MMA) levels, can result in anemia, delayed growth, and neurological impairments. This study aimed to assess the number of patients with functional vitamin B12 deficiency following ileal resection in infancy.

Methods and results
In this retrospective cohort study, patients undergoing ileal resection in their first year of life between 1996 and 2024 were included. Surgical data and laboratory results were retrieved from medical records. Functional vitamin B12 deficiency was defined as elevated MMA levels, according to age-specific cut-offs, at any point during follow-up.
Of 209 infants who underwent ileal resection, 48 (23%) died within one year. MMA levels were available in our hospital for 35 patients (22%), revealing functional vitamin B12 deficiency in 23 patients (66%) during a median follow-up duration of 7.9 years (IQR 3.8–13.0). Median time to first elevated MMA measurement was 6.9 years (IQR 3.7–10.3). Patients with functional B12 deficiency had a greater median length of ileum resected (20 cm, IQR 11–39) compared to those without deficiency (12 cm, IQR 5–23, p=0.04). 16 of the 20 patients (80.0%) with functional deficiency had normal serum B12 levels.

Conclusion / discussion
Functional vitamin B12 deficiency is common following ileal resection in infancy and may develop years after surgery. It is frequently not measured or may be overlooked by serum B12 testing alone, emphasizing the importance of long-term MMA monitoring to ensure timely diagnosis and prevent severe complications.

Keywords
Pediatrics, abdominal surgery, absorption, vitamin B12, ileum

Voluntary running and estrous cycle modulate /\ FOSB in the suprachiasmatic nucleus of the Wistar rat



Ayano Shiba
Netherlands institute for Neuroscience, Amsterdam UMC

Andries Kalsbeek
Netherlands institute for Neuroscience, Amsterdam UMC

Background and objective
/\FOSB, a stable transcription factor linked to long-term plasticity and behavioral changes, accumulates with repetitive neuronal stimulation. Voluntary wheel running, a self-reinforcing activity in rats, increases /\ FOSB in brain regions like the striatum and hippocampus, but its effects on the SCN were unknown.

Methods and results
We housed male and female Wistar rats with or without running wheels for four weeks and quantified SCN /\FOSB-positive cells. In addition, the co-staining with other SCN markers were performed to confirm the co-localization.
Unexpectedly, voluntary running lowered the number of /\FOSB-positive cells in both sexes (P = 0.069 males, P = 0.018 females). This finding was confirmed in an independent female cohort (P = 0.053). Running distance did not correlate with /\FOSB suppression.
In sedentary females, /\FOSB levels cycled with the estrous phase, peaking in diestrus and lowest in proestrus. This rhythmicity disappeared in runners, whose /\FOSB levels remained similar to proestrus levels in sedentary controls.

Conclusion / discussion
These results suggest that voluntary running and the estrous cycle influence SCN /\FOSB, potentially linking physical activity to circadian and behavioral adaptations.

Keywords
Voluntary wheel running; Exercise; Circadian rhythm; SCN; brain clock; Immediate early gene

Poster Session

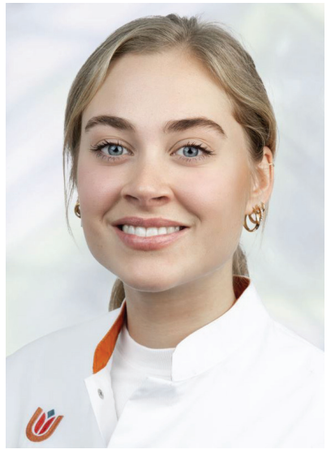
16:45-17:45

‘t Speuld

Poster Sessions | ‘t Speuld

Maaike van Bree	Protein Transition in Hospitalized Patients: Assessing Intake and Amino Acid Scores
Esmée Hoen	Transcriptomic profile of macrophages with a dominant negative mutation in the thyroid hormone receptor alpha
Melisa Emel Ermert	NAD+ and its byproducts prevent galactose-induced cell death of Complex I deficient fibroblasts
Eva Vermeer	Adverse Events of Methotrexate in Paediatric Inflammatory Bowel Disease: A Retrospective Cohort Study
Nikki van der Kruk	Microbially Conjugated Bile Acids as Potential Predictive Biomarkers for Dietary Therapy Outcomes in Paediatric Crohn’s Disease
Shacara Blake	Though men, healthy guts: A cross-sectional survey on the role of masculinity in the Curaçao colorectal cancer (CRC) screening program.
Xinru Zhang	Regulation of thyroid hormone metabolism by HNF4A via modulation of deiodinase activity in hepatocytes
Lotte Slooter	Development and internal validation of a clinical prediction model for transplant-free survival in autoimmune hepatitis.
Han Jiao	Limited microglial metabolic improvement with time-restricted feeding in diet-induced obesity
Maud Janssens	Stepwise dose escalation at start of enzyme replacement therapy for Fabry disease prevents infusion-associated reactions but does not prevent formation of anti-drug antibodies
Lauri Borghuis	Treatment response and survival of patients with early onset colorectal cancer in the Netherlands
Pascale Schafrat	Small intestinal malignancies in the Netherlands
Maaike Hogerwerf	Patient-reported long-term gastrointestinal outcomes in patients who underwent surgery for malrotation and volvulus
Joyaditya Saha	Niche-mimicry or nimicry: Molecular and mechanistic insights into the self-sustained growth of poor prognosis colorectal cancers
Deni van Schie	Microenvironmental contributions to therapy resistance and stemness in esophagogastric adenocarcinoma
Moyan Liu	A natural metabolite, 6-BromoTryptophan, to attenuate adiposity and inflammation in obesity
Nadia Romp	The gut commensal Intestinimonas butyriciproducens ameliorates obesity and associated metabolic complications in a murine model of obesity and type 2 diabetes
Ilaria Micallo	Structural basis for substrate selectivity by site-one protease revealed by studies with a small molecule inhibitor
Ashwin Mak	Obesity-associated fatty acids drive antibody-induced inflammation of macrophages via increased Fc RIII expression
Adriana Passadouro	Integrated multi-omics ingsights into substrate preference and mitochondrial dysfunction in Barth syndrome cardiac tissue
Isabelle Holscher	Challenging preoperative a-blockade in pheochromocytoma surgery: beyond tradition, towards “safer surgery ”
Alisa Allais	MicroHelath-Human Trial 1
Youling Hao	Gut microbiota-derived metabolites to halt obesity and type 2 diabetes development
Kenneth Overberg	Isoform-Specific HDAC Inhibition in Myeloid Cells Using Esterase-Sensitive Motif Technology
Karen Vermeulen	Identification of suppressors of mitochondrial stress induced by proteotoxic damage
Lente Blok	Effect of inulin supplementation on glycaemic control and immunological parameters in type 1 diabetes

Protein Transition in Hospitalized Patients: Assessing Intake and Amino Acid Scores



Maaike van Bree
Nutrition & Dietetics, Endocrinology & Metabolism, Internal Medicine, Amsterdam UMC

Maarten Soeters
Endocrinology & Metabolism, Internal Medicine, Amsterdam UMC

Background and objective
By 2026, the Green Deal Sustainable Healthcare aims for a plant-derived protein (PDP) intake of at least 50%. However, the lack of Essential Amino Acids (EAAs) in individual PDP sources presents a challenge for hospital patients. This observational study investigates the intake of plant and animal proteins in relation to EAAs in a large academic hospital.

Methods and results
Observational data on the food intake of non-critically ill adult patients were collected between October and November 2023. EAAs were determined for individual meals and scored based on the amount of EAA in milligrams per gram of protein relative to the EAA requirement. Scores =1 were considered sufficient. For data analysis, patients were divided into two groups according to the Green Deal targets: PDP = 50% vs. PDP < 50% of total protein intake.
In total, 234 patients were included (mean age 60 $\pm$ 16 years, 55% male, protein requirements 85g $\pm$ 16). Between the two groups a 23% mean difference in total protein intake was found: PDP = 50% (N=42) vs. PDP < 50% (N=192) (50g $\pm$ 22 vs. 65g $\pm$ 29). When multiple PDP sources were combined in a single meal, the EAA profile per gram of protein was sufficient.

Conclusion / discussion
Complete amino acid profiles for single meals are feasible if there is diversity in plant-derived protein sources. However, the low protein content of plant-derived products poses a challenge for hospital patients adopting a more plant-derived diet.

Keywords
Plant-derived protein, Essential Amino Acids, Green Deal Sustainable Healthcare, Protein intake, Hospitalized patients

Transcriptomic profile of macrophages with a dominant negative mutation in the thyroid hormone receptor alpha

Esmée Hoen
Endocrine Laboratory, Department of Laboratory Medicine, Amsterdam Gastroenterology, Endocrinology & Metabolism (AGEM), Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands

Anita Boelen
Endocrine Laboratory, Department of Laboratory Medicine, Amsterdam Gastroenterology, Endocrinology & Metabolism (AGEM), Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands

Background and objective
Macrophages are immune cells with many functions, ranging from fighting infections (pro-inflammatory) to immune modulation (anti-inflammatory). Moreover, these versatile phagocytes are thyroid hormone (TH) target cells. Beside the necessary TH transporters and TH activating enzymes, macrophages possess the nuclear TH receptor alpha (TRa), through which the active TH triiodothyronine (T3) acts. Here, we analyzed the transcriptomic effects of a mutated TRa in macrophages.

Methods and results
We generated bone marrow derived macrophages (BMDMs) from wild type (WT) and transgenic mice with a mutation in the T3 binding domain of the TRa (TRaPV). Naïve BMDMs (M0) were polarized into pro-inflammatory M1 (using LPS + interferon-gamma) or immunomodulatory M2 (using IL-4) phenotypes. Using RNA from M0, M1 and M2 WT and TRaPV BMDMs, RNA sequencing (RNAseq) was performed.
RNAseq analysis showed many differentially expressed genes (based on an adjusted p-value of 0.05), including 2973 genes in M0, 2112 genes in M1 and 674 genes in M2 TRaPV BMDMs compared to WT. This includes both up and down regulated genes. We found genes that have already been established as TH target genes, but we also identified novel TH-regulated genes. Additionally, increased anti-inflammatory associated gene expression was found in M1 and M2 TRaPV BMDMs.”
Conclusion / discussion
Our data show that M0, M1 and M2 TRaPV BMDMs display profoundly altered gene expression profiles. We also showed that reduced TH signaling via TRa results in increased expression of anti-inflammatory (M2) genes in M1 and M2 BMDMs, indicating that TRa-T3 action plays a role in the pro-inflammatory response of macrophages.

Keywords
Thyroid, RNAseq, macrophages

NAD+ and its byproducts prevent galactose-induced cell death of Complex I deficient fibroblasts

Melisa Emel Ermert
1. Laboratory Genetic Metabolic Diseases, Amsterdam UMC, University of Amsterdam, Amsterdam Gastroenterology, Endocrinology, and Metabolism, Amsterdam Cardiovascular Sciences, Amsterdam, The Netherlands
2. Khondrion B.v., Nijmegen, The Netherlands

Riekelt Houtkooper
Laboratory Genetic Metabolic Diseases, Amsterdam UMC, University of Amsterdam, Amsterdam Gastroenterology, Endocrinology, and Metabolism, Amsterdam Cardiovascular Sciences, Amsterdam, The Netherlands

Background and objective
The reliance of in vitro cultured cells on glycolysis for energy production even in the presence of oxygen is known as the Crabtree effect. Culturing cells in a galactose-based medium instead of glucose can overcome this effect by forcing the cells to rely on oxidative phosphorylation for energy. This method is commonly used to screen for compounds that enhance the viability of cells with defective oxidative phosphorylation system (OXPHOS) in the galactose-based medium. Recently, it has been shown that treatment with ß-NAD+ prevents galactose-induced cell death (GiCD) of Complex I-deficient patient-derived fibroblasts by restoring the cells’ redox balance. This finding prompted us to test the NAD+ precursors in this assay system.

Methods and results
Control and patient fibroblasts are cultured in glucose-free galactose-containing medium. Control cells grow slowlier whereas patient cells do not survive in this condition. Cells are treated with various compounds. Cell viability is assessed at 72 hours post-treatment.

Conclusion / discussion
Supplementation with nicotinamide (NAM), nicotinamide mononucleotide (NMN), and nicotinamide riboside (NR) did not prevent GiCD except with Nicotinic acid/Niacin (NA). Interestingly, GiCD was also blocked by the addition of structural byproducts of ß-NAD+: adenosine monophosphate (AMP), adenosine as well as ß-NAD+ itself. When we tested guanosine in addition to adenosine, we observed the same pronounced effect. We concluded that GiCD of Complex I deficient cells could be the result of a disturbed energy metabolism and purine biosynthesis instead of redox imbalance which different compounds could overcome.

Keywords
Fibroblast, OXPHOS, galactose, NAD+, purine

Adverse Events of Methotrexate in Paediatric Inflammatory Bowel Disease: A Retrospective Cohort Study

Eva Vermeer
1. Department of Paediatric Gastroenterology, Emma Children’s Hospital, Amsterdam University Medical Centre, Amsterdam, The Netherlands.
2. Amsterdam Gastroenterology Endocrinology Metabolism (AGEM) Research Institute, Amsterdam University Medical Centre, Amsterdam, The Netherlands.
3. Amsterdam Reproduction & Development (AR&D) Research Institute, Amsterdam University Medical Centre, Amsterdam, The Netherlands.

Tim de Meij
1. Department of Paediatric Gastroenterology, Emma Children’s Hospital, Amsterdam University Medical Centre, Amsterdam, The Netherlands.
2. Amsterdam Gastroenterology Endocrinology Metabolism (AGEM) Research Institute, Amsterdam University Medical Centre, Amsterdam, The Netherlands.
3. Amsterdam Reproduction & Development (AR&D) Research Institute, Amsterdam University Medical Centre, Amsterdam, The Netherlands.

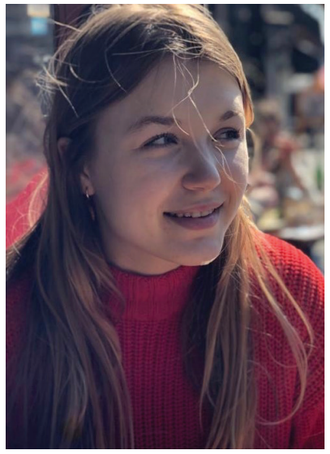
Background and objective
Methotrexate (MTX) therapy requires regular laboratory monitoring to detect adverse events (AEs) such as hepatotoxicity and myelotoxicity. However, data on the incidence of these AEs in paediatric inflammatory bowel disease (IBD) are limited. This study evaluates the incidence of MTX-induced AEs and identifies associated risk factors in paediatric IBD.

Methods and results
A retrospective monocentre cohort study included 208 paediatric IBD patients initiating MTX at Amsterdam UMC between 2010 and 2023. Data were collected on hepatotoxicity, myelotoxicity, and gastrointestinal (GI) side effects. AEs were graded per Common Terminology Criteria for Adverse Events. Incidence rates were calculated, and regression analyses identified predictors of AEs.
Among 208 patients (179 CD, 18 UC, 10 IBD-U), 111 (53,4%) used MTX as an immunomodulator alongside a biological. 66.5% received MTX orally, and 33.5% received subcutaneous MTX. Hepatotoxicity occurred in 85 patients (40.1%), mostly grade 1 (n = 52, 63.4%), with 10 cases (12.2%) of grade 3 toxicity. Myelotoxicity occurred in 43 patients (20.7%), primarily mild (n = 35, 83.3%), and no severe cases were observed. GI side effects were reported in 95 patients (45.7%). MTX was permanently discontinued in 24 patients (11.5%) due to hepatotoxicity, 2 (1.0%) for myelotoxicity, and 35 (16.8%) for GI side effects. Female sex and higher MTX dose were predictors of hepato-/myelotoxicity, while female sex and subcutaneous administration predicted GI AEs.

Conclusion / discussion
Our findings indicate that severe MTX-induced AEs in paediatric IBD are uncommon, and that MTX-related AEs rarely necessitate therapy cessation. Female sex, MTX dosage, and subcutaneous administration were significant predictors of MTX-induced AEs.

Keywords
Paediatric inflammatory bowel disease, methotrexate, adverse events, toxicity, monitoring

Microbially Conjugated Bile Acids as Potential Predictive Biomarkers for Dietary Therapy Outcomes in Paediatric Crohn's Disease



Nikki van der Kruk
1. Department of Paediatric Gastroenterology and Nutrition, Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands
2. Tytgat Institute for Liver and Intestinal Research, Amsterdam Gastroenterology, Endocrinology Metabolism (AGEM), Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands
3. Amsterdam Reproduction and Development research institute, Amsterdam, The Netherlands

Johan van Limbergen
1. Department of Paediatric Gastroenterology and Nutrition, Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands
2. Tytgat Institute for Liver and Intestinal Research, Amsterdam Gastroenterology, Endocrinology Metabolism (AGEM), Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands

Background and objective
Crohn's disease (CD) exclusion diet with partial enteral nutrition (CDED+PEN) and exclusive enteral nutrition (EEN) effectively induce remission in mild-to-moderate paediatric CD. This has been associated with a shift in gut microbiome and metabolome. The specific mechanisms driving diet-induced remission remain unclear. Microbial biotransformation of bile acids (BAs) has gained increased attention, as three novel microbially-conjugated bile acids (MCBAs) have been found in significantly higher concentrations in CD patients. We aimed to investigate changes in these MCBAs, specifically Phenylalanocholic acid (Phe-CA), Tyrosocholic acid (Tyr-CA), and Leucocholic acid (Leu-CA), associated with dietary therapies in paediatric CD.

Methods and results
BAs and MCBAs concentrations at baseline (W0) and week 6 (W6) were quantified using high performance liquid chromatography in available faecal samples from 23 treatment-naive mild-to-moderate-paediatric CD patients receiving either CDED+PEN (n=12) or EEN (n=11) in a prior RCT. Clinical remission was defined as Pediatric Crohn's Disease Activity Index (PDCAI) =10.
At W6, 19/23 patients achieved remission. Phe-CA was detected in most samples (19/23 at W0, mean=1.609μM; 12/17 at W6, mean=0.937μM). None of the samples contained detectable levels of Tyr-CA, while only one sample contained detectable Leu-CA. Among CDED+PEN patients, baseline Phe-CA was significantly higher in those who did not achieve remission vs. those who achieved remission at W6 ($p<0.0001$).

Conclusion / discussion
Baseline faecal Phe-CA concentration may serve as a predictive biomarker for CDED+PEN induced remission in paediatric CD. These findings underscore the potential significance of MCBAs in CD and dietary therapies. However, validation in a larger, prospective study is necessary to elucidate the relationship among MCBAs, CD, the microbiome, and diet-induced remission.

Keywords
IBD, Crohn's Disease, Dietary Therapies, Paediatric Gastroenterology, Microbiome

Though men, healthy guts: A cross-sectional survey on the role of masculinity in the Curaçao colorectal cancer (CRC) screening program.

Shacara Blake
Caribbean Prevention Center (Fundashon Prevenshon), Willemstad, Curaçao | Department of Gastroenterology and Hepatology, Amsterdam University Medical Center, Amsterdam, the Netherlands |Amsterdam Gastroenterology, Endocrinology and Metabolism (AGEM), Amsterdam, the Netherlands

Mirjam Fransen
Department of Public and Occupational Health, Amsterdam University Medical Center, Amsterdam, The Netherlands |Amsterdam Public Health Research Institute, Quality of Care and Digital Health, Amsterdam, The Netherlands |Department of Behaviour and Health, Centre for Prevention, Lifestyle and Health, National Institute for Public Health and the Environment, Bilthoven, the Netherlands

Background and objective
In Curaçao, men participate half as often as women in colorectal cancer (CRC) screening. Conformity to masculine norms may influence participation. We aimed to assess the association between men's conformity to masculinity and screening intention, attitudes towards CRC, cancer worry, self-rated health and CRC risk perception.

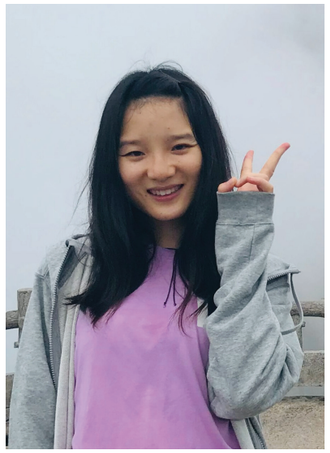
Methods and results
Questionnaires were collected from men (50-75 years) in Curaçao, through personal distribution and snowball sampling. Conformity to masculinity was measured using the Conformity to Masculine Norms Inventory-30 (CMNI-30). Self-rated health, attitude towards CRC, cancer worry, and CRC risk perception were also measured using validated items. T-tests assessed mean differences in CMNI-30 scores. Logistic regression determined association between CNMI-30 score and CRC screening intention. Linear regression assessed the association of CMNI-30 score with other variables.

Of 109 men, 83% reported a positive screening intention. Conformity to masculine norms was moderate, mean CMNI-30 75.2$\pm$11.3 (30-150). CMNI-30 score was not significantly associated with screening intention (OR: 1.02; 95% CI: 0.97-1.06). Overall, 89% of the men had a positive attitude towards CRC screening and 75% rated their health as "good". Higher CMNI-30 score was significantly associated with lower CRC risk perception ($P = 0.03$) and higher cancer worry ($P = 0.006$).

Conclusion / discussion
The men in this study showed moderate conformity to masculine norms, high CRC screening intention and no association between the two. Higher conformity to masculine norms was correlated with lower CRC risk perception and higher cancer worry. These factors should be considered when developing materials to support men in making informed screening decisions.

Keywords
Masculinity, Colorectal cancer, colorectal cancer screening, screening intention, attitude, cancer worry

Regulation of thyroid hormone metabolism by HNF4A via modulation of deiodinase activity in hepatocytes



Xinru Zhang
Endocrine Laboratory, Department of Laboratory Medicine, Amsterdam Gastroenterology, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands

Anita Boelen
Endocrine Laboratory, Department of Laboratory Medicine, Amsterdam Gastroenterology, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands

Background and objective
Metabolic dysfunction-associated steatotic liver disease (MASLD) comprises a spectrum ranging from hepatosteatosis through steatohepatitis to fibrosis and irreversible cirrhosis. Hepatocyte nuclear factor 4A (HNF4A) plays a central role in regulating hepatic lipid metabolism. Previously, we identified type 1 iodothyronine deiodinase (DIO1) as a crucial metabolic regulator in the progression of MASLD. We hypothesized that HNF4A may regulate DIO1 activity, thereby influencing thyroid hormone regulated gene expression in hepatocytes. We examined the effects of HNF4A on DIO1 activity and T3 responsive genes in a HepG2 cell with an inducible overexpression or knockdown of HNF4A.

Methods and results
For HNF4A overexpression, HepG2 cells were transfected with a doxycycline-inducible myc-tagged HNF4A transgene. For HNF4A knockdown, HepG2 cells were transiently transfected with HNF4A siRNA to reduce HNF4A mRNA expression. DIO1 activity was measured using HPLC with a radioactive rT3 tracer, and DIO1 and T3 responsive gene expression was quantified by RT-qPCR. Overexpression of HNF4A resulted in a strong increase in DIO1 mRNA expression and DIO1 activity compared to control cells. This was accompanied with increased expression of T3 responsive genes. In contrast, knockdown of HNF4A mRNA in HepG2 cells led to a significant decrease in DIO1 mRNA expression and DIO1 activity along with reduced expression of most T3 responsive genes.

Conclusion / discussion
This study shows that HNF4A is a potent regulator of DIO1 in hepatocytes. The alterations in DIO1 are associated with contradictory changes in the expression of T3 responsive genes. It is clear that HNF4A plays a role in regulating thyroid hormone concentrations via DIO1 in the hepatocyte.

Keywords
MASLD, HNF4A, DIO1, thyroid hormone, hepatocytes

Development and internal validation of a clinical prediction model for transplant-free survival in autoimmune hepatitis.

Lotte Slooter
Department of Gastroenterology and Hepatology, Amsterdam UMC, AGEM Institute, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands.

Ynte de Boer
Department of Gastroenterology and Hepatology, Amsterdam UMC, AGEM Institute, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands.

Background and objective
Autoimmune hepatitis (AIH) has various prognostic factors linked to mortality. We aim to develop and internally validate a prediction model for transplant-free survival in AIH, incorporating complete biochemical response (CBR) at 12 months.

Methods and results
We included patients with follow-up data from the International AIH Group Retrospective Registry. The endpoint was overall mortality or liver transplantation. Using backward selection, we developed the model and assessed performance with the C-index and calibration curve. Internal validation with 250 bootstrap samples updated the model coefficients.

With a median follow-up of 8 years, we included 1139 AIH patients, of whom 159 died or underwent transplantation. Among them, 42.4% did not achieve CBR at 12 months. The final model includes age, cirrhosis, non-Caucasian ethnicity, variant syndrome with PSC, and absence of CBR. It demonstrated a C-index of 0.885, with internal validation yielding 0.879 and a coefficient slope of 0.932. The prognostic index formula is:

PI = (0.034 × Age) + (0.960 × Ethnicity) + (1.430 × Cirrhosis) + (1.343 × PSC) + (1.601 × CBR)
Age: age in years at diagnosis of AIH
Ethnicity: non-Caucasian = 1; Caucasian = 0
Cirrhosis: cirrhosis at diagnosis = 1; no cirrhosis at diagnosis = 0
PSC: PSC at diagnosis = 1; no PSC at diagnosis = 0
CBR: No CBR within 12 months = 1; CBR within 12 months = 0
Survival(10y) = 1 – exp(–(0.049147616 × exp(PI)))

Conclusion / discussion
This internally validated model reliably predicts AIH survival and may support clinical decision-making.

Keywords
Prediction; autoimmune hepatitis; survival; cirrhosis; treatment response

Limited microglial metabolic improvement with time-restricted feeding in diet-induced obesity

Han Jiao
Department of Endocrinology and Metabolism, Amsterdam University Medical Centers, University of Amsterdam, The Netherlands.

Chun-Xia Yi
Department of Endocrinology and Metabolism, Amsterdam University Medical Centers, University of Amsterdam, The Netherlands.

Background and objective
Time-restricted eating has shown promise for improving metabolic health in obese humans via incompletely resolved mechanisms.

Methods and results
In this study, we investigated how time-restricted feeding (TRF) at different times of the day affects microglial immunometabolism using Wistar rats.

Conclusion / discussion
We found that in high-fat diet (HFD)-fed obese rats, TRF during the active phase reduced fat mass, altered rhythmicity of the microglial transcriptome, and prevented an increase in hypothalamic microglia. These effects were dampened or absent with TRF during the resting phase. However, a HFD-induced microglial immunometabolic phenotype, characterized by reduced electron transport chain and increased lipid metabolism gene expression, and metabolic inflexibility, was not reversed by TRF in either the active or resting phase, indicating that reprogrammed microglial metabolism in obesity is a persistent cellular functional change that requires further study.

Keywords
Microglia; High-fat diet; Time-restricted feeding; Immunometabolism; Circadian rhythm

Poster Session (16:45-17:45) | ‘t Speuld

Stepwise dose escalation at start of enzyme replacement therapy for Fabry disease prevents infusion-associated reactions but does not prevent formation of anti-drug antibodies

Maud Janssens
1. Department of Endocrinology and Metabolism, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands
2. Amsterdam Gastroenterology Endocrinology and Metabolism, Inborn Errors of Metabolism Amsterdam, the Netherlands

Mirjam Langeveld
1. Department of Endocrinology and Metabolism, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands
2. Amsterdam Gastroenterology Endocrinology and Metabolism, Inborn Errors of Metabolism Amsterdam, the Netherlands

Background and objective
Fabry disease (FD) is a rare, X-linked lysosomal storage disorder. Male patients with the classical FD phenotype are at risk of developing anti-drug antibodies (ADAs) against enzyme replacement therapy (ERT, recombinant a-Galactosidase A (a-GAL A)). The presence of ADAs is linked to infusion-associated reactions (IARs) and inhibited activity of recombinant a-GAL A (iADAs), lowering ERT effectiveness. The objective is to evaluate an adjusted ERT initiation protocol, developed to induce immune tolerance.

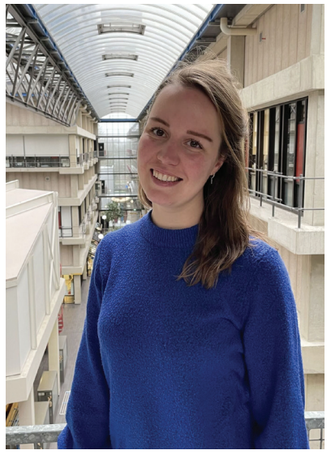
Methods and results
In the Amsterdam UMC, since June 2020, the risk of developing iADAs is determined for classical male FD patients (prediction model Van der Veen et al., 2020). Patients at high risk followed the adjusted ERT initiation protocol: stepwise dose and infusion rate increase. The control group consisted of classical male FD patients with a high risk for developing iADAs who initiated ERT between 2014 and 2020, following standard ERT initiation protocol.

None of the patients in the intervention group experienced IARs (0/7), compared to half of the patients in the control group (5/9, p=0.034). The proportion of patients developing iADAs was not different between the intervention group (4/6) and the control group (6/9, p=1). In seropositive patients, no difference was seen in the level of iADA titers (adjusted protocol: median 181 [range 34-1588], standard protocol: median 48 [range 13-193], p=0.17).

Conclusion / discussion
The adjusted ERT initiation protocol offers a solution to prevent IARs in classical male FD patients who are at high risk of developing iADAs. However, it does not prevent the development of iADAs.

Keywords
Fabry disease, lysosomal storage disorder, antibodies, infusion associated reactions, enzyme replacement therapy

Treatment response and survival of patients with early onset colorectal cancer in the Netherlands



Lauri Borghuis
Laboratory of Experimental Oncology and Radiobiology, Cancer Center Amsterdam, Amsterdam UMC and University of Amsterdam, Amsterdam, the Netherlands. Oncode Institute, Amsterdam, The Netherlands. Amsterdam Gastroenterology Endocrinology Metabolism, Amsterdam, the Netherlands.

Tineke Buffart
Laboratory of Experimental Oncology and Radiobiology, Cancer Center Amsterdam, Amsterdam UMC and University of Amsterdam, Amsterdam, the Netherlands. Amsterdam UMC, Department of Medical Oncology, Amsterdam, The Netherlands.

Background and objective
The incidence of patients with sporadic early-onset colorectal cancer (eoCRC) (<50 years) is increasing. Despite likely different tumor biology and suggestions of more aggressive disease, treatment is similar to older patients. The aim of this study was to investigate treatment response and survival in patients with eoCRC compared to matched data of older-onset (oo)CRC.

Methods and results
Clinicopathological data of all pMMR eoCRC patients diagnosed between 2016 and 2022 were requested from the NCR. Additionally matched data from patients between 50-70 and =70 years were requested. Matching was performed on tumor stage, RAS/BRAF mutation status, tumor sidedness and systemic therapy. Overall survival was analyzed.
In total 2850 patients with eoCRC and matched data from 2622 and 2009 ooCRC patients aged 50-70 and =70 were retrieved. The 5-year OS was 68%, 66% and 55% for patients <50, 50-70 and =70 years of age, respectively (p <0.001). Median OS for patients with metastatic disease at diagnosis was 24, 23 and 19 months for patients <50, 50-70 and =70 years (p <0.001). Of eoCRC patients, 46% had a RAS mutation and 10% a BRAF mutation. Best response to first line treatment was 2% complete remission, 63% partial remission, 14% stable disease, 1% mixed response and 20% progressive disease (ns).

Conclusion / discussion
EoCRC patients have similar response rates to first line systemic treatment compared to matched ooCRC patients. Although eoCRC patients more often received irinotecan and anti-EGFR therapy compared to ooCRC, the OS for eoCRC was similar to patients aged 50-70.

Keywords
Colorectal Cancer, eoCRC, ooCRC, pMMR, Overall Survival

Small intestinal malignancies in the Netherlands

Pascale Schafrat
1 Laboratory of Experimental Oncology and Radiobiology, Cancer Center Amsterdam, Amsterdam UMC and University of Amsterdam, Amsterdam, The Netherlands
2 Amsterdam Gastroenterology Endocrinology Metabolism, Amsterdam, The Netherlands
3 Oncode Institute, Jaarbeursplein 6, 3521 AL Utrecht, The Netherlands.
4 Department of Medical Oncology, Amsterdam UMC, Amsterdam, the Netherlands.

Louis Vermeulen
1 Laboratory of Experimental Oncology and Radiobiology, Cancer Center Amsterdam, Amsterdam UMC and University of Amsterdam, Amsterdam, The Netherlands
2 Amsterdam Gastroenterology Endocrinology Metabolism, Amsterdam, The Netherlands
3 Oncode Institute, Jaarbeursplein 6, 3521 AL Utrecht, The Netherlands.
4 Department of Medical Oncology, Amsterdam UMC, Amsterdam, the Netherlands.

Background and objective
Background: Small intestinal malignancies are rare, although the global incidence is rising. Therefore, knowledge about the presence and changing incidence rates of different malignant morphologies is of importance for treatment strategies and prognoses.

Methods and results
Methods: This nationwide retrospective cohort study from the Netherlands Cancer Registry included all patients diagnosed with a malignancy of the small intestine in the Netherlands between 2000 and 2022. Malignancies were divided into seven subgroups; adenocarcinomas, neuroendocrine neoplasms (NENs), gastro intestinal stromal cell tumors (GISTs), lymphomas, sarcomas, metastases and others. Age-standardized incidence rates, overall- and relative survival were reported.

Results: A total of 11.194 patients were studied for morphological subtype of small intestinal malignancy. Age-standardized incidence rates (reported in 100.000 person-years) more than doubled between 2000 and 2022 (1.88 to 3.94, p<0.001), with the largest increase of NENs (0.53 to 1.57, p<0.001), followed by adenocarcinomas (0.78 to 1.22, p=0.004) and GISTs (0.14 towards 0.53, p<0.001). The age-standardized incidence of lymphomas was more or less stable (0.32 to 0.46, p=0.088) and of sarcomas showed a decrease (0.10 to 0.02, p=0.005). There has been no significant improvement in overall survival for adenocarcinomas and NENs, in contrast to the observed increase in overall survival for lymphomas and GISTs.

Conclusion / discussion
Conclusion: The incidence of small intestinal malignancies has more than doubled in The Netherlands over two decades, mostly due to NENs and adenocarcinomas. Nonetheless, survival outcomes of these patient groups did not show improvement, and further studies towards these rare cancer types are urgently warranted.

Keywords
Small intestinal malignancies, rare cancers, epidemiology

Patient-reported long-term gastrointestinal outcomes in patients who underwent surgery for malrotation and volvulus

Maaike Hogerwerf
Amsterdam UMC, University of Amsterdam, Pediatric Surgery, Pediatric gastroenterology & Nutrition, Amsterdam, The Netherlands

Joep Derikx
Amsterdam UMC, University of Amsterdam, Pediatric Surgery, Amsterdam, The Netherlands

Background and objective
Malrotation is a congenital anomaly of the midgut which can be complicated by volvulus. Both are known for short-term gastrointestinal sequalae. Long-term gastrointestinal outcomes are less well documented. This study aimed to assess patient-reported long-term gastrointestinal symptoms in patients who underwent surgery for malrotation or volvulus compared to healthy controls.

Methods and results
In this cross-sectional study, all malrotation and volvulus patients who underwent surgery between 1997-2022 were invited to complete the Pediatric Quality of Life Inventory™ (PedsQL™) GI Module consisting of twelve domains. The PedsQL™ includes parent proxy-reports and child self-reports. Scores were transformed to a 0-100 scale, with lower scores indicating worse symptoms. Mean scores and standard deviations(SD) were compared to predefined healthy controls (n=513 , 46.2% male, mean age 11.4 years(±4.3)) using a Welch’s t-test, with Bonferroni correction applied for multiple testing.

In total, 43/167 (25.7%) respondents completed the questionnaire: 21 had malrotation (61.9% male, mean age 12.4 years(±6.7)), and 22 had malrotation with volvulus (63.6% male, mean age 12.3 years(±7.7)). The mean total score on the PedsQL™ GI Module for malrotation was 85.0(±13.0) and for volvulus 89.7(±7.5), which were comparable to healthy controls (88.6(±12.9), p=0.230 and p=0.523). Both malrotation patients and volvulus patients scored similar on the individual domains compared to healthy controls (table1).

Conclusion / discussion
Patient after malrotation and volvulus surgery reported similar long-term gastrointestinal symptoms compared to healthy controls. These findings are reassuring and can be used to guide parenteral counseling and to structure follow-up.

Keywords
Patient-reportes outcome measurements, malrotation, volvulus, long-term outcomes, gastrointestinal

Niche-mimicry or nimicry: Molecular and mechanistic insights into the self-sustained growth of poor prognosis colorectal cancers

Joyaditya Saha
Amsterdam UMC, Vrije Universiteit Amsterdam, Laboratory of Experimental Oncology and Radiobiology (LEXOR), Amsterdam, The Netherlands

Louis Vermeulen
Amsterdam UMC, Vrije Universiteit Amsterdam, Laboratory of Experimental Oncology and Radiobiology (LEXOR), Amsterdam, The Netherlands

Background and objective
Colorectal cancer (CRC) is the third most prevalent cancer worldwide. Four molecular subtypes of CRC referred to as the consensus molecular subtypes (CMSs) are currently defined, with the poor-prognosis mesenchymal CMS4 subtype predominantly contributing to peritoneal metastases (PMs). Despite the abundance of activated stroma in CMS4 tumors, we observe that compared to the other subtypes, CMS4 CRC cells are significantly less dependent on either the presence of fibroblasts or additional growth factors for their proliferation. These observations suggest that CMS4 CRC cells can produce factors enabling themselves to be niche-independent and self-sustaining through autocrine (self) interactions, which we investigate further in the project. We term this phenomenon as niche-mimicry or nimicry.

Methods and results
Using the CellPhoneDB cell-communication algorithm on both single cell and bulk RNA sequencing data, we established that the number of self-interactions (SIs) or autocrine ligand-receptor pairs in CMS4 CRCs is markedly higher compared to the other subtypes. Furthermore, by comparing correlations between transcription factor (TF) activity and SIs across multiple datasets, we identified the TEAD family of transcription factors as master regulators of SIs which we validated via follow-up in vitro and in vivo experiments.

Conclusion / discussion
We therefore present nimicry as a theoretical framework that explains the clinical and molecular characteristics of CMS4 CRCs. Our findings indicate that inhibition of TEAD TFs could serve as an effective therapeutic intervention for the treatment of CMS4 CRCs.

Keywords
Colorectal, cancer, subtypes, autocrine, interactions

Microenvironmental contributions to therapy resistance and stemness in esophagogastric adenocarcinoma

Deni van Schie
Laboratory of Experimental Oncology and Radiobiology, Cancer Center Amsterdam, Amsterdam UMC, Amsterdam, the Netherlands

Maarten Bijlsma
Laboratory of Experimental Oncology and Radiobiology, Cancer Center Amsterdam, Amsterdam UMC, Amsterdam, the Netherlands

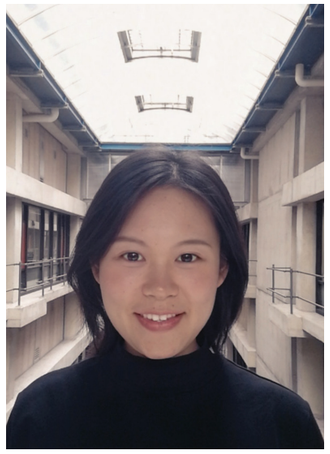
Background and objective
Esophageal adenocarcinoma (EAC) incidence is rising in the West, yet survival remains poor due to therapy resistance. Cancer-associated fibroblasts (CAFs), a prominent component of the tumor microenvironment, are known to regulate tumor progression, therapy resistance, and stemness. In esophageal cancer, CAF abundance has been linked to cancer progression and poor patient survival, however CAF heterogeneity and their specific contributions to EAC remain underexplored. We hypothesize that distinct CAF subsets can be identified in EAC and that the tumor-promoting activities of these subsets converge on driving tumor stemness.

Methods and results
This study integrates single-cell and single-nucleus RNA sequencing (sc/snRNAseq) datasets from multiple sources to resolve fibroblast-specific signatures, creating an atlas of CAF subtypes. This enables the deconvolution of bulk RNA sequencing data from a large, well-annotated EAC cohort. This approach links CAF subtypes to key clinical outcomes such as patient survival, therapy resistance, and tumor progression. Preliminary analyses have identified inflammatory (iCAF), myofibroblast-like (myCAF), and vascular-like (vCAF) CAF phenotypes, each associated with distinct biological pathways and prognostic implications. Imaging mass cytometry (IMC) will validate the spatial organization of CAF subsets and their dynamics following neoadjuvant chemoradiation. Functional studies in minitumor models will evaluate their roles in tumor-stroma interactions and clonal growth.

Conclusion / discussion
This work aims to clarify CAF heterogeneity’s clinical significance in EAC. Combining single-cell and bulk RNA analyses identifies actionable CAF targets, enabling therapies that disrupt tumor-promoting CAF functions while preserving protective roles. These insights could improve EAC treatment outcomes by targeting stromal drivers of resistance and stemness.

Keywords
Cancer-associated fibroblasts, esophageal adenocarcinoma, scRNAseq integration, bulk RNA deconvolution, therapy resistance

A natural metabolite, 6-BromoTryptophan, to attenuate adiposity and inflammation in obesity



Moyan Liu
Department Experimental Vascular Medicine, Amsterdam University Medical Center (AUMC, Location AMC), Amsterdam Gastroenterology Endocrinology Metabolism (AGEM) Research Institute, Amsterdam Cardiovascular Science (ACS) Institute, 1105AZ Amsterdam, The Netherlands.

Elena Rampanelli
Department Experimental Vascular Medicine, Amsterdam University Medical Center (AUMC, Location AMC), Amsterdam Gastroenterology Endocrinology Metabolism (AGEM) Research Institute, Amsterdam Cardiovascular Science (ACS) Institute, 1105AZ Amsterdam, The Netherlands.

Background and objective
The global rise in obesity and associated Type 2 Diabetes represents a significant public health challenge. Growing evidence highlights the pivotal role of dietary derivatives and plasma metabolites in the etiology of metabolic diseases.
Using plasma untargeted metabolomics, we identified a halogenated derivative of dietary tryptophan, 6-bromotryptophan (6-BT), as a potential beneficial metabolite associated with lower body mass index (BMI) and improved lipid profiles in obese individuals.

Methods and results
Prompted by promising clinical observations, we investigated the effects of 6-BT in a severe obesity and diabetes model (db/db mice). For this, db/db mice were treated with intraperitoneal injections of placebo or 20 mg/kg 6-BT at 8 weeks of age, when obesity and hyperglycemia are already present. After a 4-week intervention, 6-BT administration was found to significantly counteract adiposity, as evidenced by decreased proportion of white adipose tissue (WAT) and reduced adipocyte hypertrophy. Additionally, 6-BT attenuated macrophage infiltration in WAT, liver, and kidney, and lowered pro-inflammatory cytokine secretion in the liver.
Mechanistic in vitro studies revealed that 6-BT exposure enhanced mitochondrial oxidative metabolism in adipocytes and hepatocytes, upregulated genes expression related to beta oxidation, and reduced intracellular lipid accumulation via AMPK phosphorylation and SIRT1 expression. Furthermore, 6-BT mitigated inflammation by inhibiting the NF-?B pathway and pro-inflammatory signaling from TNF-a and IL-6.

Conclusion / discussion
Collectively, our findings highlight the potential of 6-BT as a natural therapeutic agent to counteract adiposity and alleviate chronic inflammation. Further studies are warranted to investigate its efficacy under diet-induced obesity conditions, explore its long-term metabolic benefits, and evaluate its translational prospect.

Keywords
6-Bromotryptophan, Obesity, Inflammation, AMPK Activation, Adiposity

The gut commensal Intestinimonas butyriciproducens ameliorates obesity and associated metabolic complications in a murine model of obesity and type 2 diabetes

Nadia Romp
Amsterdam UMC, Universiteit van Amsterdam, Experimental Vascular Medicine, Amsterdam, The Netherlands

Elena Rampanelli
Amsterdam UMC, Universiteit van Amsterdam, Experimental Vascular Medicine, Amsterdam, The Netherlands

Background and objective
The gut microbiome has been found to shape inflammatory and metabolic processes through host-microbiota interactions via various bacteria-derived metabolites. This study focuses on the newly isolated gut commensal strain I. butyriciproducens for its unique ability to convert dietary fructoselysine into butyrate, a signaling molecule with anti-obesogenic and anti-inflammatory properties. Fructoselysine, a prevalent Amadori product and precursor of advanced glycation end-products linked to metabolic disorders, is abundant in the Western diet and forms through the thermal heating of food. Furthermore, in a human cohort study using fecal metagenomic analysis, I. butyriciproducens and its fructoselysine fermentation genes were found to be negatively associated with BMI, triglycerides, HbA1c, and fasting insulin levels. The hypothesis posits that I. butyriciproducens, partly through butyrate production, protects against obesity and metabolic dysfunction.

Methods and results
This study therefore investigates the role of I. butyriciproducens in fructoselysine metabolism and its contribution to metabolic diseases by utilizing a diet-induced obesity mouse model that mimics metabolic syndrome. Oral administration of I. butyriciproducens resulted in attenuated body weight gain, adiposity, and hyperglycemia. Moreover, I. butyriciproducens treatment reduced inflammation and enhanced browning of adipose tissue and insulin signaling in inguinal white adipose tissue. These outcomes may be partly attributed to the bacterial strain’s ability to convert fructoselysine into butyrate, leading to elevated plasma and cecal butyrate levels, which contribute to systemic effects.

Conclusion / discussion
Overall, I. butyriciproducens has been found to ameliorate obesity and associated metabolic complications in a murine model of obesity and type 2 diabetes, emphasizing its therapeutic potential for preventing or treating metabolic diseases.

Keywords
Micobiome, obesity, diabetes, cardiometabolic, butyrate

Structual basis for substrate selectivity by site-one protease revealed by studies with a small molecule inhibitor

Ilaria Micallo
Amsterdam UMC, Universiteit van Amsterdam, Medical Biochemistry, Amsterdam, The Netherlands

Noam Zelcer
Amsterdam UMC, Universiteit van Amsterdam, Medical Biochemistry, Amsterdam, The Netherlands

Background and objective
Site-one protease (S1P) carries out the first proteolytic step to activate membrane-bound effector proteins in the Golgi. S1P matures through an autocatalytic process that begins in the endoplasmic reticulum (ER) and culminates with the displacement of its inhibitory pro-domain by its co-factor, SREBP-regulating gene (SPRING). Spatial control of S1P activity and substrate localization underpins signaling pathways governing, amongst others, lipogenesis, ER stress, and lysosome biogenesis. The factors governing these pathways are activated by S1P-mediated proteolysis upon their regulated transport from the ER to the Golgi. The structural basis for substrate recognition by S1P has remained unknown.

Methods and results
Here, we used the small molecule PF-429242, a competitive inhibitor of S1P, to investigate substrate recognition by the S1P/SPRING complex. We designed an S1P mutation (I308A) to reduce the steric clash and generated an S1P that was resistant to PF-429242 in cell culture assays. We also identified a catalytically dead mutant (N348A) that was not able to activate the SREBP pathways.

Conclusion / discussion
Our findings reveal new selectivity in the recognition of substrates by S1P and provide a roadmap to the rational design of improved S1P inhibitors.

Keywords
Lipids, metabolism, MAFLD, inhibitor, molecular

Obesity-associated fatty acids drive antibody-induced inflammation of macrophages via increased Fc RIII expression

Ashwin Mak
Center for Infection and Molecular Medicine, Amsterdam UMC, Amsterdam, the Netherlands

Jeroen den Dunnen
Center for Infection and Molecular Medicine, Amsterdam UMC, Amsterdam, the Netherlands

Background and objective
Obesity is a major risk factor for inflammatory diseases and poorer disease outcome in severe infections, such as COVID-19. Anti-SARS-CoV-2 spike IgG antibodies are known to be a key trigger in COVID-19 hyperinflammation, eliciting excessive macrophage activation through IgG receptor (Fc?R) signaling in severe COVID-19. However, the role of obesity in exacerbating Fc?R-mediated hyperinflammation remains unexplored. Here, we hypothesize that prolonged exposure to obesity-associated fatty acids amplifies antibody-induced inflammation, contributing to the poor disease outcomes in obese individuals.

Methods and results
To simulate the metabolic environment of obesity, monocyte-derived macrophages were differentiated in the presence of palmitate, with non-palmitate-exposed macrophages serving as controls. Hereafter, these macrophages were stimulated with viral components and anti-SARS-CoV-2 spike-IgG complexes to mimic the in vivo conditions where macrophages encounter viruses and antigen-IgG-antigen during infection.

Palmitate-treated macrophages stimulated with anti-spike IgG show significantly increased production of pro-inflammatory cytokines (IL-6, TNF, IL-1ß) compared to control macrophages. Notably, this heightened inflammatory response was absent with viral stimulation alone, underscoring the critical role of palmitate in amplifying IgG-dependent inflammation. In line with this, palmitate-treated macrophages demonstrated elevated Fc?RIII expression, and blocking of Fc?RIII resulted in a significant reduction in cytokine production.

Conclusion / discussion
Our findings suggest a novel mechanism which obesity-associated metabolic disturbances amplify antibody-induced inflammation in obese individuals. We show that palmitate exposure amplifies Fc?R-mediated macrophage activation, offering insights into why obese individuals experience more severe inflammation in conditions such as COVID-19. Beyond infectious diseases, these findings may have broader implications for hyperinflammatory disorders associated with immune complexes.

Keywords
Macrophages, antibodies, obesity, inflammation, COVID

Integrated multi-omics ingsights into substrate preference and mitochondrial dysfunction in Barth syndrome cardiac tissue

Adriana Passadouro
1. Laboratory Genetic Metabolic Diseases, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands
2. Amsterdam Cardiovascular Sciences, Amsterdam, The Netherlands
3. Amsterdam Gastroenterology, Endocrinology and Metabolism, Amsterdam, The Netherlands
4. Department of Physiology, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands.

Riekelt H. Houtkooper & Signe Mosegaard
1. Laboratory Genetic Metabolic Diseases, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands
2. Amsterdam Cardiovascular Sciences, Amsterdam, The Netherlands
3. Amsterdam Gastroenterology, Endocrinology and Metabolism, Amsterdam, The Netherlands
4. Emma Center for Personalized Medicine, Amsterdam, The Netherlands

Background and objective
Barth syndrome (BTHS) is a rare X-linked recessively inherited disorder caused by variants in the TAFAZZIN gene. The pathogenic variants lead to impaired conversion of monolysocardiolipin (MLCL) into matured phospholipid cardiolipin (CL). The accumulation of MLCL and mature CL deficiency is a diagnostic marker for BTHS. The clinical spectrum includes cardiomyopathies, skeletal myopathies, neutropenia, and delays in growth and development. In severely affected BTHS patients, the cardiac phenotype is early onset, heterogeneous and unpredictable. Ultimately, these patients may require a cardiac transplantation early in their life. Unfortunately, the pathophysiological mechanisms of BTHS are poorly understood, and treatment options for BTHS remain symptomatic.

Methods and results
In this study, we investigated a unique collection of heart samples from five paediatric male BTHS individuals (5 month-15 years old) and compared them to tissues from 24 non-failing donors (19-71 years old) using a newly developed integrated omics method that combines metabolomics, lipidomics and proteomics in a single sample.

This comprehensive analysis confirms expected changes in established diagnostic markers such as CL and MLCL, as well as severe and pleiotropic alterations in mitochondrial phenotype and metabolic output, a substrate shift in energy metabolism, and an elevation of heart-failure markers. It also reveals striking interindividual differences between BTHS individuals.

Conclusion / discussion
Combined, we describe a powerful analytical tool for the in-depth analysis of metabolic disorders and a solid foundation for the understanding of BTHS disease phenotypes in cardiac tissues.

Keywords
Multi-omics, cardiac tissue, cardiomyopathy, mitochondrial dysfunction

Challenging preoperative a-blockade in pheochromocytoma surgery: beyond tradition, towards “safer surgery”

Isabelle Holscher
Department of Surgery, Amsterdam UMC, University of Amsterdam, The Netherlands

Els J.M. Nieveen van Dijkum
Department of Surgery, Amsterdam UMC, University of Amsterdam, The Netherlands

Background and objective
The dramatic decline of mortality and morbidity associated with pheochromocytoma surgery over the past decades is frequently attributed to the introduction of perioperative alpha-adrenergic blockade. Therefore, preoperative alpha-blockade is traditionally considered necessary. However, evidence for this correlation is lacking, since the influence of preoperative alpha-blockade has never been tested in a randomized trial. The aim of this national survey was to explore the design of a future clinical trial that examines perioperative care for patients with pheochromocytoma.

Methods and results
A survey was sent to specialized physicians involved in pheochromocytoma care in The Netherlands. The survey consisted of questions regarding the current perioperative protocols, patient eligibility, study design and outcome measures. Twenty-three responses from 8 centers were included (response rate of 71.9%). Of the respondents, 8 (35%) were endocrine surgeons, 7 (30.5%) were endocrinologists and 7 (30.5%) were anesthesiologists. The preferred study design for the future clinical trial is a randomized controlled trial with a non-inferiority design. While opinions on preferred outcome measure and selection criteria for patient eligibility were more heterogeneous, there was consensus that clinical outcome measures should be incorporated into the study, and exclusion of patients should be limited to cases with a significantly higher risk of developing perioperative complications.

Conclusion / discussion
The diverse perspectives regarding study design and perioperative anticipated risks, alongside the predominant monodisciplinary focus of current guidelines led by endocrinologists, emphasize the necessity of a multidisciplinary approach in future research, particularly when conducting randomized controlled trials.

Keywords
Pheochromocytoma, adrenalectomy, survey, alpha-blockade

MicroHelath-Human Trial 1

Alisa Allais
Amsterdam UMC locatie AMC, Experimental Vascular Medicine, Amsterdam, The Netherlands

Hilde Herrema, Max Nieuwdorp
Amsterdam UMC locatie AMC, Experimental Vascular Medicine, Amsterdam, The Netherlands

Background
Diet shapes the gut microbiome; by providing essential nutrients, which sustain the existing microorganisms and by introducing foodborne microbes that modulate its composition.

Hypothesis
Differences in agricultural practices, organic vs conventional strategies, can lead to variations in nutritional content and associated microbial communities in and on crops, influencing the human gut microbiome’s composition and function.

Research plan
Primary objective is the measurements of glucose metabolism and its relation to the gut microbiome composition and function. Additionally, measurments of blood metabolomics, health markers and pesticides residues.

Anticipated results
After three weeks of dietary intervention a different gut microbiome composition and function is anticipated between the organic and conventional groups.

Keywords
Gut Microbiome, Nutrition, Diet, Agricultural Strategies, Human Intervention Trial

Gut microbiota-derived metabolites to halt obesity and type 2 diabetes development

Youling Hao
Amsterdam UMC, University of Amsterdam, Amsterdam Cardiovascular Science Research Institute, Amsterdam Gastroenterology Endocrinology Metabolism Research Institute, Amsterdam institute for Immunology and Infectious Diseases, Amsterdam, The Netherlands

Elena Rampanelli
Amsterdam UMC, University of Amsterdam, Amsterdam Cardiovascular Science Research Institute, Amsterdam institute for Immunology and Infectious Diseases, Amsterdam, The Netherlands

Background
With obesity being a global epidemics, associated metabolic diseases constitute an ever growing public-health threat. Over the past decades, growing evidence show that perturbations in gut microbiota structure and function are among the risk factors that contribute to obesity and metabolic syndrome, opening novel avenues for therapeutic interventions.
Indeed, gut microbiota is now recognized as the cross-road of host-environment interactions with a key role in regulating host metabolism through a close cross-talk between peripheral tissues and circulating microbiota-derived metabolites.
Using untargeted metabolomics and machine learning analysis, we recently identified two microbially-produced metabolites, phenylacetylglutamine (PAG) and phenylacetylcarnitine (PAC), which associated with improved metabolic heath in obese individuals and were found increased after microbiota transplantation from vegan donors.

Hypothesis
PAG and PAC suggest a positive effect on the host metabolism and health.

Research plan
Using in vitro assays, we discovered that PAC and PAG influence the expression of key genes involved in oxidative metabolism and lipid biosynthesis. Moreover, both metabolites boosted white adipocyte oxidative mitochondrial metabolism in white adipocytes.Based on these findings, we will further explore the effects of PAG and PAC in obesity using the diet-induced obesity murine model and weekly intraperitoneal administrations of PAG/PAC over a period of 12 weeks. Primary read-outs include changes in weight-gain, adipose tissue weight and adipocyte size, liver steatosis and insulin sensitivity.

Anticipated results
We hypothesize that PAC and PAG may exert beneficial effects in antagonizing lipid accumulation and hence counteract adiposity and type 2 diabetes development.

Keywords
Gut metabolites, obesity, type 2 diabetes

Isoform-Specific HDAC Inhibition in Myeloid Cells Using Esterase-Sensitive Motif Technology

Kenneth Overberg
Amsterdam UMC, Universiteit van Amsterdam, Tytgat Institute for Liver and Intestinal Research, Amsterdam, The Netherlands

Wouter de Jonge
Amsterdam UMC, Universiteit van Amsterdam, Tytgat Institute for Liver and Intestinal Research, Amsterdam, The Netherlands

Background
Histone deacetylases (HDACs) regulate chromatin remodeling and gene expression by removing covalently bound acetyl groups from proteins and DNA. HDACs are active in various mechanisms, and their dysregulation is implicated in multiple diseases, including inflammatory bowel disease (IBD)1. Broad-spectrum HDAC inhibitors often cause adverse events, primarily due to the broad-spectrum activity of HDACs and untargeted distribution in the body2. An esterase-sensitive motif (ESM) that can couple to compounds, allowing for selective myeloid cell targeting due to their human carboxylesterase-1 expression, was developed3, reducing the risk of adverse events and increasing ESM-coupled compounds’ effects. To date, no isoform-specific ESM-HDACi have been developed. We aim to establish an isoform-specific ESM-HDAC X inhibitor as a potential therapeutic strategy for inflammation and IBD.

Hypothesis
Novel ESM-enhanced HDAC X inhibitors were synthesized and evaluated using human peripheral blood mononuclear cells treated with increasing concentrations of compounds, followed by lipopolysaccharide stimulation. Using enzyme-linked immunosorbent assay analysis, IL-6 and TNF-a production was measured to assess the compounds’ anti-inflammatory activity, with ESM-non-targeting compound as a control.

Research plan
One compound significantly reduced IL-6 after one (2.5μM: $p<0.01$; 5 μM: $p<0.001$) and three hours (2.5μM: $p<0.05$; 5 μM: $p<0.01$) and TNF-a after one hour (5 μM: $p<0.05$) of pretreatment, proving more potent than HDAC x inhibitor.

Anticipated results
Using genetic and biochemical tools, the cytotoxicity, isoform specificity, and myeloid cell-specific delivery will be determined. Their therapeutic potential will be evaluated in preclinical inflammation models, including colitis models. These studies aim to establish ESM-based HDAC X inhibitors as a novel therapeutic strategy with minimal adversities.

Keywords
IBD, Myeloid cells, HDACs, ESM, CES-1

Identification of suppressors of mitochondrial stress induced by proteotoxic damage

Karen Vermeulen
Amsterdam UMC, Universiteit van Amsterdam, Gastroenterology and Hepatology, Amsterdam, The Netherlands

Noam Zelcer
Amsterdam UMC, Universiteit van Amsterdam, Gastroenterology and Hepatology, Amsterdam, The Netherlands

Background
The mitochondrion has emerged as a key player in protein homeostasis by counteracting aggregated amyloid-beta occurring in Alzheimer’s Disease (AD). The mitochondrial stress response (MSR), induced in AD patients, is essential to prevent excessive mitochondrial damage and protein aggregation. To understand the underlying mechanisms, this PhD project will elucidate how mitochondria are linked to proteostasis and their impact on AD.

Hypothesis
The expectation is to identify suppressors of mitochondrial stress induced by proteotoxic damage.
Research plan
A stable neuronal cell-line will be generated that overexpresses amyloid precursor protein (APP) containing the Sweden mutation (APPswe), known for enhancing Aß aggregation. Mitochondrial stress suppressors will be identified by performing a CRISPR/Cas9 driven methodology of genome-wide functional genetic screen. To allow for a screening-based strategy, a readout will be used to determine the status of mitochondrial membrane potential and content, which decreases during Aß proteotoxic stress. Identified suppressors will be validated to determine their effect on mitochondrial function and protein aggregation. Pharmacological compounds that may target the identified pathways will also be assessed in in vitro and in vivo models to investigate if they modify the AD pathology.

Anticipated results
This genetic screening will represent a novel, effective and unbiased method to uncover suppressors of mitochondrial stress induced by proteotoxic damage. In this setup, a recovery in mitochondrial homeostasis might possibly depend also on the identification of pathways that lead to reduced Aß proteotoxicity. Therefore, this approach will also allow the indirect identification of negative regulators of both cellular proteostasis and mitochondrial stress.

Keywords
Mitochondrial dysfunction, Alzheimer’s Disease, Protein aggregation, CRISPR/Cas9 screening, mitochondrial stress response

Poster Session (16:45-17:45) | ‘t Speuld

Effect of inulin supplementation on glycaemic control and immunological parameters in type 1 diabetes

Lente Blok
Amsterdam UMC, AMC, Internal vascular medicine, Amsterdam, The Netherlands

dr Nordin Hanssen
Amsterdam UMC, AMC, Internal vascular medicine, Amsterdam, The Netherlands

Background
Type 1 diabetes (T1D) is a complex autoimmune disease involving both genetic and environmental factors. To date exogenous insulin replacement therapy is the only available treatment, demonstrating a clear need for a broadly applicable additional therapy. Fermentable fibres, such as inulin, are an area of extensive research, driven in part by growing understanding of the systemic effects of their fermentation products, short-chain fatty acids (SCFAs), which have a plethora of immunological and metabolic effects, as well as their evident glucose-lowering effects in type 2 diabetes. However, no clinical trial assessing immunological and glycemic effects of inulin in adults with T1D has been performed.

Hypothesis
We hypothesize that inulin as aonce-daily supplement of 10g will improve continuous glucose monitoring (CGM) metrics compared to placebo, and thus may represent a much-needed therapeutic option for achieving optimal glycaemic control in T1D.

Research plan
A double-blind, randomized, placebo-controlled trial with 2 arms (n= 38 per arm) in which we will establish the effect of oral inulin supplementation for 12 weeks on CGM-metrics and immunological parameters in adults with T1D, with a time in euglycemic range of <80%.

Anticipated results
The main study endpoint is the difference in time in range between the groups between baseline and end-of-study, in which we will expect increased time in range in the treatment group. Secondary endpoints include changes in glycaemic variability, gut microbiome composition, changes in urinary C-peptide-to-creatinine-ratio (beta cell function), changes in immunological parameters and validated questionnaires (Quality of Life and gastro-intestinal complaints).

Keywords
Type 1 diabetes, gut microbiome, fermentable fiber, glycemic control, beta cell function

Friday

Session C

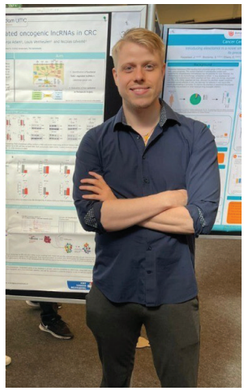
09:15-10:00

Plenary session
‘t Speuld

Session C | ‘t Speuld

Oscar Bril & Sophie Vromans	Comprehensive CRISPR/Cas9 tiling of a human chromosome
Shihui Zheng	Identifying novel therapeutic targets for Gyrate Atrophy
Rona Brokkelkamp	The effect of hormone replacement therapy on glucose regulation in postmenopausal women with diabetes
Femke Mol	Decreased CD8A and CD8B expressing blood T cell populations may predict adalimumab and infliximab response failure in Crohn’s disease patients
Kelly van Wijnbergen	DECIPHER study

Comprehensive CRISPR/Cas9 tiling of a human chromosome



Oscar Bril en Sophie Vromans
1. LEXOR, Cancer Center Amsterdam and Amsterdam Gastroenterology Endocrinology Metabolism, Amsterdam UMC, Research & Diagnostiek Centrum ADORE Van der Boechorstraat 6B, 1081 BT, Amsterdam, the Netherlands
2. Oncode Institute, Research & Diagnostiek Centrum ADORE Van der Boechorstraat 6B, 1081 BT Amsterdam, The Netherlands

Nicolas Léveillé
1. LEXOR, Cancer Center Amsterdam and Amsterdam Gastroenterology Endocrinology Metabolism, Amsterdam UMC, Research & Diagnostiek Centrum ADORE Van der Boechorstraat 6B, 1081 BT, Amsterdam, the Netherlands 2. Oncode Institute, Research & Diagnostiek Centrum ADORE Van der Boechorstraat 6B, 1081 BT Amsterdam, The Netherlands

Background
Deep functional understanding of the human genome remains a central challenge in molecular biology, unequivocally curtailing knowledge translation. Finding novel disease-specific vulnerabilities is a crucial step towards the development of new therapeutic strategies. This is particularly urgent in the context of colorectal cancer, the fourth most commonly diagnosed cancer and the second cause of cancer death worldwide, which recent estimates predict an increase of colon (71.5%) and rectal cancer (60%) cases by the year 2035.

Hypothesis
We hypothesize that a refined mapping of crucial DNA sequences throughout the human genome will uncover a vast amount of vulnerabilities, which could be translated into novel therapeutic approaches.

Research plan
Thus, we aim to initiate this task by tiling (designing 1 guide/100 nucleotides) an entire human chromosome with complementary CRISPR/Cas9 gRNA libraries, using dropout screens as a readout, and a colorectal cancer cell line as a cellular model. We expect that tiling chromosomes will precisely map crucial genomic sequences distributed across essential protein-coding genes, non-coding RNAs, unknown transcripts, regulatory elements (e.g. promoters, enhancers, introns) and structural components (e.g. CTCF), which support optimal cancer cells fitness.

Anticipated results
Uncovering these essential elements will facilitate the creation of novel therapeutic approaches.

Keywords
CRISPR-Cas Genomics CRC Oncology Discovery

Identifying novel therapeutic targets for Gyrate Atrophy

Shihui Zheng
Amsterdam UMC, University of Amsterdam, Department of Human Genetics, Amsterdam, the Netherlands.

Arthur A Bergen
1. Amsterdam UMC, University of Amsterdam, Department of Human Genetics, Section Ophthalmogenetics, Amsterdam, the Netherlands
2. Amsterdam UMC, University of Amsterdam, Department of Ophthalmology, the Netherlands
3. Amsterdam UMC, Emma Center for Personalized Medicine, the Netherlands.

Background
Gyrate Atrophy of the Choroid and Retina (GACR; OMIM: 258870) is a rare autosomal recessive disorder caused by mutations in the OAT (ornithine aminotransferase) gene, resulting in the toxic accumulation of ornithine. This metabolic imbalance drives progressive retinal degeneration, ultimately leading to severe vision loss or blindness. While dietary arginine restriction is currently employed to reduce ornithine levels, this approach is only partially effective and does not halt the underlying disease progression, emphasizing the urgent need for novel therapeutic strategies.

Hypothesis
Promising targets identified through screening will be validated in our patient-derived induced pluripotent stem cell (iPSCs) models, to confirm their therapeutic potential. Validation studies will assess key cellular and metabolic outcomes such as ornithine levels, oxidative stress and overall cell viability, ensuring that the therapeutic impact of these targets is effective and disease-relevant.

Research plan
This project aims to identify therapeutic targets that mitigate ornithine toxicity and restore metabolic balance in GACR. Using CRISPR-based functional genomic screening in OAT knockout ARPE-19 cells, we seek to systematically uncover genes and pathways that enhance cellular resilience to elevated ornithine levels.

Anticipated results
By integrating advanced functional genomics with patient-derived preclinical cell models, this project seeks to establish a pipeline for the discovery and validation of novel therapeutic targets for GACR. This approach not only paves the way for the development of new effective therapies for this rare disorder but could also provide a framework for addressing other metabolic diseases with limited treatment options.

Keywords
GACR, iPSC, ornithine, metabolism pathway, screening

The effect of hormone replacement therapy on glucose regulation in postmenopausal women with diabetes

Rona Brokkelkamp
1. Amsterdam UMC Location University of Amsterdam, Department of Endocrinology and Metabolism, Amsterdam, The Netherlands
2. Research Institute, Amsterdam Gastroenterology Endocrinology and Metabolism, Amsterdam, the Netherlands.

Sarah Siegelaar
1. Amsterdam UMC Location University of Amsterdam, Department of Endocrinology and Metabolism, Amsterdam, The Netherlands
2. Research Institute, Amsterdam Gastroenterology Endocrinology and Metabolism, Amsterdam, the Netherlands.

Background
Glycaemic control is crucial in diabetes management to prevent diabetes-related complications. The menopausal transition, characterized by estrogen depletion, might influence glycaemic control. Estrogen depletion leads to metabolic changes, including the accumulation of visceral fat and an increase in insulin resistance. These metabolic changes result in an increased risk of cardiovascular disease in postmenopausal women compared to premenopausal women.
Hormone Replacement Therapy (HRT) can partially mitigate these metabolic changes. When used within the first 10 years of menopause, HRT has been shown to reduce all-cause mortality and cardiovascular disease. Additionally, HRT is suggested to have a beneficial effect on glucose regulation and insulin resistance in postmenopausal women with type 2 diabetes. However, no studies have been conducted on the effects of HRT in postmenopausal women with type 1 diabetes."

Hypothesis
Transdermal 17-ß-estradiol supplementation in combination with micronized progesterone improves glucose regulation in postmenopausal women with diabetes. Secondary, HRT had an positive effect on cardiovascular risk, liver steatosis, menopausal complaints, and, (diabetes-related) quality-of-life.

Research plan
We will conduct a single centre, cross-over, double-blind, placebo-controlled clinical trial, investigating the effect of transdermal 17-ß-estradiol versus placebo in women with diabetes after menopause on glucose regulation and secondary outcome parameters. The study will have a duration of 28 weeks: two intervention periods of 12 weeks each with a four week wash-out period in between.

Anticipated results
We expect that the use of 12 weeks HRT improves time-in-range by 5 percent compared to placebo.

Keywords
Diabetes, Menopause, Hormone Replacement Therapy, glucose regulation

Decreased CD8A and CD8B expressing blood T cell populations may predict adalimumab and infliximab response failure in Crohn's disease patients

Femke Mol
Amsterdam UMC, University of Amsterdam, Tytgat Institute for Liver and Intestinal Research, Amsterdam, The Netherlands

Wouter de Jonge
1. Amsterdam UMC, University of Amsterdam, Tytgat Institute for Liver and Intestinal Research, Amsterdam, The Netherlands
2. University Clinic of Bonn, Department of Surgery, Bonn, Germany

Background and objective
Mainstream biological treatment for Crohn's disease (CD) anti-tumor necrosis factor (anti-TNF) therapies, adalimumab and infliximab, are effective in inducing and maintaining remission in patients with Crohn's disease. Nonetheless, up to 40% of CD patients fail to respond, emphasizing the need to characterize the molecular differences predicting response failure. This study aimed to assess predictive biomarkers for treatment efficacy.

Method and results
The EPIC-CD cohort included 57 adult CD patients starting adalimumab or infliximab. Treatment response was evaluated after 6-9 months using endoscopic, biochemical, and clinical criteria. Whole peripheral blood leukocytes were collected before treatment and at response assessment. mRNA was extracted, sequenced, and analyzed for differential expression. DNA methylome was quantified and analyzed for differential methylation. Cell type deconvolution was performed using both gene expression and DNA methylation data. Differential gene expression analysis revealed significantly higher expression of CD8A and CD8B in responders to both adalimumab and infliximab before treatment. Transcriptional pathways associated with cytotoxic activity were enriched in responders. Cell type deconvolution based on gene expression and DNA methylome measurements suggested higher CD8T cell proportions in responders.

Conclusion/discussion
Our data suggest that non-response to anti-TNF therapy may be associated with lower CD8T populations compared to responders. This aligns with emerging evidence highlighting the heterogeneity and prognostic potential of CD8T subsets in inflammatory bowel disease. Further research is needed to validate these observations and explore their functional implications for personalized therapeutic approaches in CD treatment.

Key words
Crohn's disease, anti-TNF, treatment response, CD8+ T cell, biomarker

DECIPHER study

Kelly van Wijnbergen
1. Department of Gastroenterology and Hepatology, Amsterdam UMC location University of Amsterdam, Amsterdam, Netherlands.
2. Amsterdam Gastroenterology Endocrinology Metabolism, Amsterdam, Netherlands.
3. Laboratory of Experimental Oncology and Radiobiology, Cancer Center Amsterdam, Amsterdam UMC and University of Amsterdam, Amsterdam, the Netherlands.
4. Oncode Institute, Amsterdam, Netherlands

Joep Grootjans
1. Department of Gastroenterology and Hepatology, Amsterdam UMC location University of Amsterdam, Amsterdam, Netherlands.
2. Amsterdam Gastroenterology Endocrinology Metabolism, Amsterdam, Netherlands.
3. Laboratory of Experimental Oncology and Radiobiology, Cancer Center Amsterdam, Amsterdam UMC and University of Amsterdam, Amsterdam, the Netherlands.
4. Oncode Institute, Amsterdam, Netherlands

Background
Immune checkpoint inhibitors (ICI) have revolutionized cancer treatment, significantly improving outcomes for patients with advanced or metastatic cancers. However, these therapies can also lead to immune-related adverse events (irAEs), such as immune-mediated colitis (IMC), which can disrupt treatment and negatively impact patients' health. Identifying predictive biomarkers for IMC susceptibility is crucial to better manage these side effects and optimize treatment.

Hypothesis
We hypothesize that the incidence and severity of IMC can be predicted by specific biomarkers, including immune cell populations, cytokine profiles, microbiome, and metabolome composition in the colon, blood, and stool before and during ICI therapy. Additionally, differences in these biomarkers may vary depending on the type of ICI treatment (anti-PD1 vs anti-CTLA-4 vs anti-PD+anti-CTLA-4).

Research plan
Patients diagnosed with cancer and treated with ICIs will undergo sigmoidoscopy with biopsies before and optionally after 12 weeks of treatment. Blood and stool samples will also be collected. We will analyze immune cell frequencies, cytokine production, microbiome, and metabolome before and during treatment, comparing patients who develop grade 3/4 IMC to those who do not using single-cell analysis methods. We will also explore differences in immune responses based on the type of ICI used.

Anticipated results
We expect to identify specific biomarkers that correlate with the development of IMC, including immune cell populations, cytokine levels, and microbiome/metabolome profiles. These findings could enable early prediction of IMC risk, helping tailor more personalized and safer ICI therapies.

Keywords
Immune checkpoint inhibitors, Immune-related adverse events (irAEs), Immune-mediated colitis (IMC), Biomarkers, Immunology

Session D

11:45-12:30

Parralel sessions

Session D1 | Verwondering

Iman Hu	Topoisomerase inhibitor amonafide enhances defense responses to promote longevity in C. elegans
Kasper T. Vinten	Comparative transcriptomic and metabolomic analyses of NAD+ precursors in cultured hepatocytes
Sibbeliene E. van den Bosch	Sex differences in cardiovascular risk among children with familial hypercholesterolemia
Jasmijn van Doesburg	INCA TRIAL: MANAGEMENT OF ADRENAL INCIDENTALOMAS IN PATIENTS WITH GASTROINTESTINAL MALIGNANCIES.
Oluwatomisono Akinrimisi	Lactobacillus delbrueckii is associated with methylglyoxal levels in type 2 diabetes

Session D2 | Levendig

Dewi van Harskamp	A combined stable isotope infusion method to assess therapeutic efficacy in primary hyperoxaluria patients
Omer Ozcan	Blood collection tubes with protease inhibitors to prevent cryoactivation of renin
Thuc-Anh Nguyen	Inhibition of hepatic bile salt uptake using the anti-HDV drug Bulevirtide attenuates inflammation in mouse models for colitis
Yannick van Schajik	MATERNAL ANTIBIOTIC PROPHYLAXIS DURING CESAREAN SECTION AFFECTS FAECAL TRYPTAMINE IN NEONATES: A SECONDARY ANALYSIS OF A RANDOMIZED CONTROLLED TRIAL
Jiarong Li	Histone Serotonylation (H3Q5ser): A Novel Epigenetic Signature in Crohn's Disease Pathogenesis

Session D3 | Fantasie

Ahmed Bayoumy	The Fate of Thiopurine Metabolites After Switching to Low-Dose Thiopurine with Allopurinol or Thioguanine in IBD Patients: A Retrospective Analysis
Serhii Chornyi	Macrophages produce lipid mediators ducring bacterial meningitis
Paul Manoukian	Estrogen production in pancreatic cancer shapes a tumor suppressive stroma
Virginia Bruno	Patient-derived gut microphysiological system to investigate the interaction between Candida albicans clinical isolates and intestinal epithelium in inflammatory bowel disease
Dana Meije	Innovative therapeutic strategies targeting NTCP for cholestatic Diseases

Session D4 | Focus

Dandan Wu	Targeting Hepatic Amino Acid Uptake to Improve Systemic Signaling and Metabolic Diseases
Lotte Oldenburg	Dose intensification of vedolizumab is not effective in inducing endoscopic response in Crohn's disease patients with endoscopic primary non-response
Tim Middelburg	The Enhanced Liver Fibrosis score and Liver Stiffness Measurement as surrogate endpoints in primary sclerosing cholangitis
Weisha Li	Plasma triacylglycerol length and saturation level mark healthy aging groups in humans
Malou Dongen	SCT- Delphi Study: Development of a Core Outcome Set for treatment of Sacrococygeal Teratoma

Topoisomerase inhibitor amonafide enhances defense responses to promote longevity in C. elegans

Iman Hu
Amsterdam UMC, Universiteit van Amsterdam, Experimental Vascular Medicine, Amsterdam, The Netherlands

Riekelt H. Houtkooper, Georges E. Janssens
Laboratory Genetic Metabolic Diseases, Amsterdam UMC, University of Amsterdam, The Netherlands; Amsterdam Gastroenterology, Endocrinology, and Metabolism Institute, Amsterdam, The Netherlands.

Background and objective
Aging is a significant risk factor for diseases. Lowering AKT1 levels is one of the key pathways related to longevity in various model organisms

Methods and results
We conducted an in silico drug screen for small molecules mimicking AKT1 knockdown and validated and explored mechanisms of candidates in C. elegans for longevity effects.

Topoisomerase inhibitors, particularly amonafide, significantly improved healthspan and lifespan in C. elegans. Amonafide's benefits were not solely DAF-16/FOXO-dependent. RNA sequencing showed a youthful transcriptional profile and activated diverse defense pathways.

Conclusion / discussion
Amonafide, a novel geroprotector, activates mitochondrial, pathogen, and xenobiotic defense responses, suggesting potential for Parkinson's therapy.

Keywords
Drug screening, geroprotector

Comparative transcriptomic and metabolomic analyses of NAD+ precursors in cultured hepatocytes

Kasper T. Vinten
1. Laboratory Genetic Metabolic Diseases, Amsterdam UMC, University of Amsterdam, The Netherlands and
2. Amsterdam Gastroenterology, Endocrinology, and Metabolism Institute, Amsterdam, The Netherlands

Riekelt H. Houtkooper
1. Laboratory Genetic Metabolic Diseases, Amsterdam UMC, University of Amsterdam, The Netherlands
2. Amsterdam Gastroenterology, Endocrinology, and Metabolism Institute, Amsterdam, The Netherlands
3. Amsterdam Cardiovascular Sciences institute, Amsterdam, The Netherlands

Background and objective
Nicotinamide adenine dinucleotide (NAD+) is a key molecule in multiple metabolic reactions acting both as a redox cofactor and a substrate for various enzyme families involved in cellular metabolism, transcriptional regulation, and DNA damage repair. Notably, a decline in intracellular NAD+ has been identified as a central phenomenon in mammalian aging, while dietary supplementation with NAD+ precursors has shown pre-clinical efficacy in preventing metabolic and age-related complications. Despite this, clinical translation of such benefits has proven a challenge due to our limited knowledge about the different properties of NAD+ precursors, their systemic availability, cellular utilization, and their impact on downstream degrading paths.

Method and results
To explore these properties, we performed RNA sequencing and metabolomics on cultured murine hepatocytes treated with nicotinamide mononucleotide (NMN), reduced NMN (NMNH), nicotinamide riboside (NR), and reduced NR (NRH). Significantly greater transcriptional and metabolomic changes were observed in reduced precursors (NMNH, NRH) compared to non-reduced precursors (NMN, NR). Shared differentially expressed genes between NMNH and NRH revealed upregulation of stress related glutathione S-transferases. However, this was not reflected by corresponding metabolite changes of the glutathione-oxiglutathione oxidative stress pathway. Enrichment analysis further indicated divergent functional effects, with NMNH prominently affecting metabolic processes, while NRH showed stronger associations with cellular processes like cell division.

Conclusion/discussion
Together, our data suggest that reduced NAD+ precursors exert a generally more pronounced impact on metabolic and transcriptomic levels compared to their non-reduced counterparts, which warrants deeper investigation for their translational potential.

Key words
NAD+ metabolism, Aging, Cellular stress, Transcriptomics, Metabolomics

Sex differences in cardiovascular risk among children with familial hypercholesterolemia

Sibbeliene E. van den Bosch MD
1. Amsterdam UMC location University of Amsterdam, Department of Pediatrics, Meibergdreef 9, Amsterdam, the Netherlands
2. Amsterdam Gastroenterology Endocrinology Metabolism research institute, Amsterdam, the Netherlands
3. Amsterdam Cardiovascular Sciences research institute, Diabetes & Metabolism, Amsterdam, the Netherlands
4. Amsterdam UMC location University of Amsterdam, Department of Epidemiology and Data Science, Meibergdreef 9, Amsterdam, the Netherlands

Albert Wiegman MD, PhD
1. Amsterdam UMC location University of Amsterdam, Department of Pediatrics, Meibergdreef 9, Amsterdam, the Netherlands
2. Amsterdam Gastroenterology Endocrinology Metabolism research institute, Amsterdam, the Netherlands
3. Amsterdam Cardiovascular Sciences research institute, Diabetes & Metabolism, Amsterdam, the Netherlands

Background and objective
Heterozygous familial hypercholesterolemia (FH) is characterized by elevated low-density lipoprotein cholesterol (LDL-C) levels from birth onwards, leading to an increased risk for premature atherosclerotic cardiovascular disease (ASCVD). The general consensus is to diagnose and treat FH from childhood. Although studies in adults have shown clinical differences in ASCVD between sexes, LDL-C goals are similar. The aim of this study is to evaluate whether sex differences in cardiovascular risk are present in children with FH.

Methods and results
For this cross-sectional study, all children (<19 years) who were referred to the lipid clinic of the Amsterdam UMC for a tentative diagnosis of FH were eligible. Patients with FH and in whom cardiovascular risk was measured by carotid intima-media thickness (cIMT) were included. Patient characteristics, medical history and lipid profiles were obtained from electronical medical records. The association between sex and cIMT was evaluated using linear regression analyses, adjusting for potential confounders.

We included 842 children with FH (median (IQR) age 13.3 (10.8 – 13.0) years), of whom 418 (49.6%) were boys. In boys with FH, mean (SD) cIMT was significantly higher compared to girls (0.463 (0.037) mm versus 0.452 (0.034) mm; respectively, p<0.001). After adjustment for potential confounders, this association remained significant (p<0.001).

Conclusion / discussion
Our findings suggest a significantly higher cardiovascular risk in boys with FH compared to girls. Further research is needed to explore the role of sex in development of premature atherosclerosis in patients with FH and results may be helpful in considering sex-specific LDL-C targets in the future.

Keywords
Children atherosclerosis cIMT familial hypercholesterolemia ASCVD

INCA trial: management of adrenal incidentalomas in patients with gastrointestinal malignancies

Jasmijn van Doesburg
Department of Surgery, Amsterdam UMC, University of Amsterdam, Gastroenterology Endocrinology Metabolism, Cancer Center Amsterdam, the Netherlands

Freek Daams
Department of Surgery, Amsterdam UMC, Vrije Universiteit Amsterdam, Cancer Center Amsterdam, the Netherlands.

Background and objective
When adrenal incidentalomas are detected during the diagnostic workup for gastrointestinal malignancies, ruling out pheochromocytoma and potential adrenal metastases is essential. Aim of this study is validating a new management protocol that also accounts for the limited time available during the diagnostic workup of oncological patients.

Methods and results
This prospective cohort study included patients with recently diagnosed upper GI, colorectal, or HPB malignancies discussed in a multidisciplinary meeting between May 1 2023 and November 1 2024 at the Amsterdam UMC. Primary outcomes were compliance, etiology and treatment delay.
In total, 1822 patients were included (mean age 68 years). Majority were male(58.2%) and had no distant metastases(M0, 69.6%). Overall, 62.6% were treated with curative intent. Adrenal incidentalomas =1 cm were identified in 132 patients (7.2%; left-sided in 54.0%; median size 15.0 mm, IQR:11.0–20.0 mm). Of these, 67 patients(50.8%) underwent unenhanced CT. For the remaining patients, additional imaging was deemed clinically irrelevant. On these scans, 13 incidentalomas showed a density >10 Hounsfield Units. Plasma metanephrines were measured in 7 patients, 4 displayed mild elevations, prompting endocrinology consultation. No statistically significant difference was found in the time from diagnosis to start treatment for patients with and without adrenal incidentaloma (Mann-Whitney U; Neoadjuvant chemo(radio)therapy combined with surgery z=-0.11, p=0.914, Surgery z=-0.80, p=0.423, Definitive chemo(radio)therapy z=-0.86, p=0.390, Palliative z=-0.78, p=0.434).

Conclusion / discussion
Clinically relevant pheochromocytomas were extremely rare, none were identified in this cohort. The new protocol was validated as a reliable tool during the diagnostic workup, without causing delay in the start of oncological treatment.

Keywords
Adrenal incidentaloma, gastrointestinal malignancy, CT, imaging, diagnostics

Lactobacillus delbrueckii is associated with methylglyoxal levels in type 2 diabetes

Oluwatomisono Akinrimisi
Department of Experimental Vascular and Internal Medicine, Amsterdam UMC

Nordin Hanssen
Department of Experimental Vascular and Internal Medicine, Amsterdam UMC

Background and objective
Methylglyoxal (MGO) is a compound formed as a byproduct of glycolysis and is known to be cytotoxic. Its formation and metabolism by prokaryotic cells has remained relatively neglected in the setting of human diseases. This study investigates the relationship between the human gut microbiome and MGO to eventually find new therapeutic targets to lower MGO.

Methods and results
A subset of the BARIA cohort was used which included 292 patients (76 % female, mean age 47 ± 10 years) with morbid obesity. Fecal metagenomics alongside targeted metabolomics (UPLC-MS/MS , MGO analysis) was used to explore the association between the gut microbiome and plasma MGO levels.

Plasma MGO was significantly higher in individuals with diabetes (295 ± 60nmol/L) compared to individuals without diabetes (252 ± 71 nmol/L) (P = 0.001). A correlation was observed between Lactobacillus delbrueckii abundance and plasma MGO in the individuals with diabetes (Spearman rho = 0.37, P-adjusted = 0.02). which persisted after adjusting for age and sex. Lactobacillus delbrueckii formed the closest clusters with Streptococcus thermophilus in both groups of individuals with and without diabetes.

Conclusion / discussion
Plasma MGO was higher in diabetes. Higher abundance of Lactobacillus delbrueckii was associated with higher plasma MGO in individuals with diabetes. In vitro experiments will be conducted to explore the causal direction of these findings.

Keywords
Microbiome , Type 2 diabetes , Glycolysis , Statistics , Metabolites

A combined stable isotope infusion method to assess therapeutic efficacy in primary hyperoxaluria patients

Dewi van Harskamp
1. Amsterdam UMC, Department of Laboratory Medicine, Core Facility Metabolomics, Laboratory Genetic Metabolic Disease, University of Amsterdam, Amsterdam, Netherlands.
2. Amsterdam UMC, Emma Center for Personalized Medicine, Amsterdam, Netherlands.
3. Amsterdam UMC, Amsterdam Gastroenterology, Endocrinology & Metabolism, Amsterdam, Netherlands.

Henk Schierbeek
Department of Pediatrics, Emma Children's Hospital Amsterdam UMC, location University of Amsterdam, Amsterdam, The Netherlands

Background and objective
To assess the efficacy of new therapies for Primary Hyperoxaluria type 1 (PH1), a novel stable isotope protocol was developed. PH1 is a rare disease caused by a deficiency of the liver enzyme AGT, leading to oxalate overproduction, urolithiasis, nephrocalcinosis, and renal failure. Previously, liver and kidney transplantation were the only curative options, but new therapies offer less invasive treatments.

Methods and results
Traditional biomarkers for PH1, such as urinary or plasma oxalate, are unreliable due to variability and prolonged washout of calcium oxalate crystals. Stable isotopes provide a precise method to evaluate new drugs and understand the glycolate/glyoxylate pathway. Using U-13C-oxalate, d5-glycine, and 1-13C-glycolate in a primed continuous infusion allows for the quantification of glycine and oxalate production and AGT function.

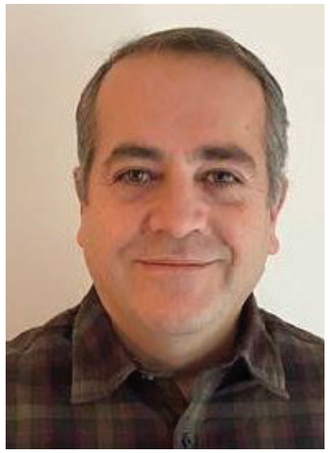
Enrichments of 1-13C-glycolate, 1-13C-glyoxylate, 1-13C-oxalate, and U-13C2-oxalate were measured in plasma using GC-MS/MS. Stable enrichment plateaus enabled calculations of production rates and specific conversions.

Conclusion / discussion
Glycolate is a key precursor of oxalate in PH1 patients but not in healthy individuals. Patients unresponsive to pyridoxine (B6-) showed virtually no AGT activity, while responsive patients (B6+) and healthy individuals had significant conversion rates. Endogenous oxalate production was higher in B6- patients compared to healthy and B6+ individuals.

This protocol can evaluate individual therapeutic efficacy, investigate pyridoxine responsiveness, and explore glyoxylate metabolism.

Keywords
Stable isotope tracing; in vivo metabolism; Primary Hyperoxaluria; Mass Spectrometry; Personalized Medicine

Blood collection tubes with protease inhibitors to prevent cryoactivation of renin



Omer Ozcan
Amsterdam UMC, Location of AMC, Clinical Chemistry, Endocrine Laboratory, Amsterdam, The Netherlands

Annemieke C. Heijboer
Amsterdam UMC, Vrije Universiteit Amsterdam, Clinical Chemistry, Endocrine Laboratory, Amsterdam, The Netherlands

Background and objective
Cryoactivation is caused by cold exposure (between 4°C and −5°C) triggering the conversion of prorenin to renin by plasma proteases. Therefore, optimal storage of plasma samples for renin analyses is challenging. Our aim was to study, the prevention of cryoactivation by blood collection tubes containing protease inhibitors, and the reversibility of cryoactivation by short-term incubation at 37°C.

Methods and results
From 24 individuals, blood samples were collected in (I) K2EDTA, (II) aprotinin, (III) trypsin inhibitor (TI) and (IV) protease inhibitor cocktail(PIC) containing tubes. Plasma samples were aliquoted and renin concentrations(RC) measured: 1) freshly, 2) after storage for one week at +4°C, 3) two weeks at -20°C and 4) at -80°C. Subsequently, samples were incubated at 37°C for 2-hours and measured again. RC were measured using an automated immunoassay (IDS-i10).
RC of samples stored at -80°C were similar to those from freshly measured samples (median differences, −7 to 0%). Increase of RC(median) were 19-50% and 61-190% in the samples stored at +4°C and -20°C, respectively, compared to RC of fresh samples. The increased concentrations after −20°C storage returned to fresh levels after incubation at 37°C when using TI and PIC tubes but not when using K2EDTA or aprotinin tubes.

Conclusion / discussion
Our study shows significant cryoactivation of renin in samples stored at -20°C freezers and it is reversed by incubation at 37°C in the samples taken into TI and PIC tubes. Using these tubes for collection of blood samples could be an alternative for laboratories who are not able to measure renin in fresh samples or without -80°C freezers to avoid cryoactivation.

Keywords
Pre-analysis, Renin, Cryoactivation, Laboratory errors, Aldosterone

Inhibition of hepatic bile salt uptake using the anti-HDV drug Bulevirtide attenuates inflammation in mouse models for colitis

Thuc-Anh Nguyen
Tytgat Institute for Liver and Intestinal Research, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands

Stan van de Graaf
Tytgat Institute for Liver and Intestinal Research, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands

Background and objective
Although activation of the bile salt receptor TGR5 leads to reduced pro-inflammatory cytokine production in macrophages and attenuated inflammation in mice, TGR5 synthetic agonists did not reach clinical application. Instead, we aimed to exploit systemic bile salt signaling by using Bulevirtide, an inhibitor of the main hepatic uptake transporter of bile salts-Na+ Taurocholate Co-transporting Polypeptide (NTCP). We investigated if NTCP inhibition could attenuate intestinal inflammation and whether TGR5 and the nuclear receptor FXR are required for bile salt-immunosuppressive effects.

Methods and results
Bulevirtide effectively increased plasma bile salt levels in mice lacking the Organic Anion Transporting Polypeptide (OATP)1a/1b genes, which resembled human (NTCP-centered) hepatic bile salt dynamics. In mice treated once with lipopolysaccharide (LPS) to induce acute inflammation, single Bulevirtide treatment reduced plasma levels of the inflammatory cytokine TNFa and increased the anti-inflammatory cytokine IL10. In a colitis model induced with 5-day dextran sodium sulfate (DSS), daily Buleviritide prevented body weight loss, attenuated intestinal damage, and reduced intestinal gene expression of inflammatory cytokines TNFa, IL1ß and IFN?. Additionally, bone marrow-derived macrophages (BMDM) from wild-type (WT), TGR5-/-, and FXR-/- mice were stimulated with LPS and treated with taurochenodeoxycholic acid (TCDCA) in vitro. TCDCA administration reduced TNFa and IL1ß secretion and this was similar between WT, TGR5-/- and FXR-/- BMDM.

Conclusion / discussion
NTCP inhibition reduces intestinal inflammation, suggesting novel clinical applications of Bulevirtide and NTCP targeting small molecules. Interestingly, the effects of bile salts on BMDM in vitro were independent of TGR5 and FXR, suggesting the involvement of additional bile salt receptors underlying the beneficial effects of NTCP inhibition.

Keywords
Bile salt signaling, bile salt transporter, inflammation, colitis, macrophages

Maternal antibiotic prophylaxis during cesarean section affects faecal tryptamine in neonates: a secondary analysis of a randomized controlled trial

Yannick van Schajik
1. Tytgat Institute for Liver and Intestinal Research, Amsterdam UMC, University of Amsterdam, Amsterdam Gastroenterology and Metabolism, Meibergdreef 69-71, 1105 BK Amsterdam, the Netherlands

Wouter J. de Jonge
1. Tytgat Institute for Liver and Intestinal Research, Amsterdam UMC, University of Amsterdam, Amsterdam Gastroenterology and Metabolism, Meibergdreef 69-71, 1105 BK Amsterdam, the Netherlands
2. Department of Surgery, University of Bonn, 53127 Bonn, Germany

Background and objective
Over 20% of global births are delivered via caesarean-section(c-section) and use prophylactic maternal antibiotics as preventive standard care to infectious complications. Effects of this treatment on neonatal intestinal microbiota development is limited, however the effects on neonatal gut metabolome remain largely unexplored. Here, we assess the effects of maternal prophylactic antibiotics on neonatal tryptophan metabolism, which affects intestinal barrier and immune functions.

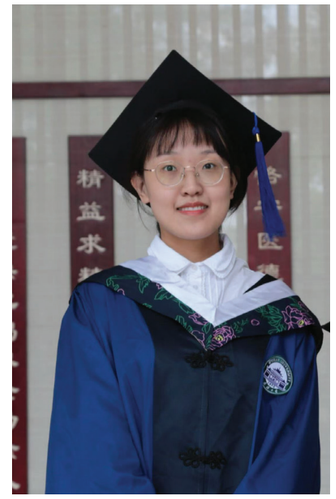
Methods and results
Faeces were collected at 1&4 weeks-of-life in C-section born neonates exposed or not to maternal prophylactic cephalosporin (nAB=32, nNoAB=16) as part of a two previous RCTs. Microbiome and metabolome were determined by shotgunsequencing & targeted tryptophan metabolomics(HPLC/MS). Microbiota-metabolite correlations were assessed by Spearman's correlation coefficients and linear models.

Microbial beta diversity showed difference based on prophylactic antibiotic exposure. Tryptamine, a microbiota-derived tryptophan catabolite was increased in antibiotic-exposed neonates compared to non-exposed C-section. It was associated with Enterococcus and Blautia families. Although not differing between the subgroups, picolinic-acid negatively correlated to maternal antibiotic levels at 1 week of life.

Conclusion / discussion
In this secondary analysis of 2 RCT cohorts, we investigated microbiota-tryptophan metabolites in C-section born neonates, with/without antibiotic prophylaxis. Although antibiotic exposure did not strongly affect microbiota, increased levels of tryptamine were observed in antibiotic-exposed neonates. A negative correlation antibiotic-concentration/picolinic-acid, associated to neurodevelopment, was observed in both RCT-cohorts. Our results suggest that antibiotic prophylaxis in C-section born neonates may impact tryptophan metabolism. Tryptamine and picolinic-acid may affect development via the brain-gut axis, follow-up studies are urgently needed to better understand long-term health impacts to early-life antibiotics exposure.

Keywords
Microbiome, antibiotics, neonatology, tryptophan metabolism

Histone Serotonylation (H3Q5ser): A Novel Epigenetic Signature in Crohn's Disease Pathogenesis



Jiarong Li
Tytgat Institute for Liver and Intestinal Research, Amsterdam Gastroenterology, Endocrinology Metabolism Amsterdam UMC, Amsterdam University, Amsterdam, The Netherlands.

Wouter de Jonge and Mohammed Ghiboub
Tytgat Institute for Liver and Intestinal Research, Amsterdam Gastroenterology, Endocrinology Metabolism Amsterdam UMC, Amsterdam University, Amsterdam, The Netherlands.

Background and objective
Elevated serotonin levels in intestinal mucosa correlate with Crohn's disease (CD) severity. Serotonin can form H3Q5ser through covalent binding to histone H3 at glutamine-5. With TGM2 (essential for serotonin-histone binding) being highly expressed in inflamed CD mucosa, we investigated H3Q5ser's role in CD pathogenesis.

Methods and results
We analyzed H3Q5ser levels in serotonin-treated PBMCs, CD patient tissues, and healthy controls (HCs) using Western blot, immunofluorescence, and flow cytometry. PBMC subtypes were compared between active CD (n=5), CD in remission (n=9), and HCs (n=7). We found that PBMCs showed dose-dependent H3Q5ser increase with serotonin treatment. CD mucosal tissues exhibited elevated serotonin and H3Q5ser levels, particularly in immune and epithelial cells. H3Q5ser+CD45+ cells were abundant in inflamed CD mucosa. CD14+ monocytes showed significantly higher H3Q5ser levels compared to other PBMC subsets. Both active and quiescent CD patients demonstrated elevated H3Q5ser levels versus HCs.

Conclusion / discussion
Our findings establish a correlation between serotonin and H3Q5ser levels, showing increased presence in CD patient tissues. H3Q5ser enrichment in CD14+ monocytes during both active and quiescent disease suggests its role in CD-related immune dysregulation. Further research on H3Q5ser's genomic locations and transcriptional effects could reveal new therapeutic targets for CD.

Keywords
Histone Serotonylation, Epigenetics, Crohn's disease, Inflammation, Monocytes

The Fate of Thiopurine Metabolites After Switching to Low-Dose Thiopurine with Allopurinol or Thioguanine in IBD Patients: A Retrospective Analysis

Ahmed B. Bayoumy
Amsterdam UMC, Vrije Universiteit Amsterdam, Gastroenterology and Hepatology, Amsterdam, The Netherlands

Nanne K.H. de Boer
Amsterdam UMC, Vrije Universiteit Amsterdam, Gastroenterology and Hepatology, Amsterdam, The Netherlands

Background and objective
Shunting (hypermethylating) thiopurine metabolism, characterized by excessive 6-MMPR production and (sub)therapeutic 6-TGN levels, poses a significant challenge in the treatment of inflammatory bowel disease (IBD). This study evaluates the metabolic outcomes of switching to low-dose thiopurine with allopurinol (LDTA) or thioguanine (TG) in IBD patients with shunting metabolism.

Method and results
This retrospective study analyzed demographic data, thiopurine metabolite profiles, and adverse event rates in shunting IBD patients before and after switching to LDTA or TG therapy. Metabolite variability was assessed by examining alterations in 6-MMPR and 6-TGN levels and their correlation before and after therapy switch.

Both therapies significantly reduced toxic 6-MMPR levels, with 100% of patients achieving non-toxic levels (6-MMPR-level below 7000 pmol/8x10E8 RBC) post-therapy. For TG, 93% of patients attained non-toxic 6-TGN levels (6-TGN < 1000 pmol/8x10E8 RBC).In contrast, LDTA showed greater variability in 6-TGN outcomes, with 50% of patients reaching therapeutic levels, 31% remaining subtherapeutic, and 19% within toxic-range. The slope for LDTA was significantly positive (1.044, R^2 = 0.4515, P = 0.004), reflecting proportional increases in 6-TGN levels.

Conclusion/discussion
Switching to LDTA or TG therapy in shunting IBD patients resulted in favorable alterations in thiopurine metabolism. However, LDTA appears to have a slightly less favorable metabolite profile, with some residual 6-MMPR formation and fewer patients achieving normal 6-TGN levels compared to TG. Given the challenges associated with achieving optimal thiopurine metabolite levels with LDTA and the need for closer monitoring of 6-TGN levels, TG appears a more suitable option for thiopurine shunting IBD patients.

Key words
Thiopurines, thioguanine, inflammatory bowel disease

Macrophages produce lipid mediators ducring bacterial meningitis

Serhii Chornyi
Amsterdam UMC, Molecular Cell Biology and Immunology. Leiden UMC, Center for Proteomic and Metabolomic

Gijs Kooij
Amsterdam UMC, department Molecular Cell Biology and Immunology

Background and objective
Unfavorable outcomes in bacterial meningitis are characterized by a dysregulated inflammatory response of the host's immune system. Polyunsaturated fatty acids-derived lipid mediators (LMs) play a fundamental role in inflammation, yet their involvement during bacterial meningitis remains unclear.

Methods and results
We have measured LMs concentrations in cerebrospinal fluid (CSF) and plasma samples from adults with community-acquired Streptococcus pneumoniae meningitis (n=74) and healthy controls (n=8) using targeted HPLC-MS/MS analysis. We detected 35 LMs that were present in CSF from pneumococcal meningitis patients but not from healthy controls, and the concentrations were higher in the patients that had an unfavourable outcome (Glasgow Outcome Scale score <5). 5-HETE, thromboxane B2, and prostaglandin E2 were particularly highly abundunt. Interestingly, thromboxane and prostaglandins were the most abundant during the first hours after the disease onset. The lipids were either not detected or were much less abundant in the plasma of the meningitis patients.

To determine the origin of lipid mediators, we co-cultured iPSC-derived microglia, astrocytes, choroid plexus papilloma, and PBMC-derived macrophages in the presence of S. pneumoniae. Only the macrophages produced lipid mediators in response to the bacteria.

Conclusion / discussion
Our study provides the first profiling of lipid mediators in patients with pneumococcal meningitis. We also present evidence that these lipids are produced by resident macrophages during the onset of the disease.

Keywords
Lipidomics, inflammation, brain, fatty acids, HPLC-MS

Estrogen production in pancreatic cancer shapes a tumor suppressive stroma

Paul Manoukian
Laboratory of Experimental Oncology and Radiobiology, Cancer Center Amsterdam, Amsterdam UMC and University of Amsterdam. Van der Boechorststraat 6b, 1081BT Amsterdam, The Netherlands

Maarten Bijlsma
Laboratory of Experimental Oncology and Radiobiology, Cancer Center Amsterdam, Amsterdam UMC and University of Amsterdam. Van der Boechorststraat 6b, 1081BT Amsterdam, The Netherlands

Background and objective
Pancreatic cancer is a leading cause of cancer-related death due to a lack of effective therapeutic interventions. An abundance of stroma is hypothesized to contribute to poor outcome. However, both tumor-promoting and -restraining stromal fibroblasts have been described and how these are instructed remains poorly understood.

Methods and results
Here, we observed that serum levels of positively prognostic stromal biomarkers were significantly higher in female PDAC patients compared to males. This was supported by in silico estimates of stromal abundance across solid cancers and magnetic resonance elastography showing that female PDAC patients had stiffer tumor tissue. Gene expression analysis revealed that estrogen signaling instructs a stromal fibroblast phenotype that is associated with relatively indolent molecular subtypes and a more favorable prognosis, which is maintained by stromal expression of C-type lectin CLEC3B. Remarkably, we could detect estrogens intra-tumorally, and found that pancreatic cancer cells express key enzymes for estrogen synthesis. We identified that estrogen production in PDAC is fueled by the catabolism of stroma-derived branched chain amino acids, which ultimately results in the production of steroid hormone precursors.

Conclusion / discussion
To reiterate, our data reveal that PDAC cell-produced estrogen impacts the surrounding CAFs. This consquently shapes a tumor-suppressive microeenvironment, which encourages indolent PDAC cell states. We believe this to be a previously unrecognized aspect of pancreas cancer biology that can provide leads for therapy development.

Keywords
Pancreatic ductal adenocarcinoma, Hormone signaling, Cancer-associated fibroblasts, Tumor-stroma interaction, Tumor endocrinology

Patient-derived gut microphysiological system to investigate the interaction between Candida albicans clinical isolates and intestinal epithelium in inflammatory bowel disease

Virginia Bruno
1. Department of Molecular Biology and Microbial Food Safety, Swammerdam Institute for Life Sciences, University of Amsterdam, Amsterdam, the Netherlands
2. Tytgat Institute for Liver and Intestinal Research, Amsterdam Gastroenterology Endocrinology Metabolism, Amsterdam University Medical Center, Location AMC, University of Amsterdam, Meibergdreef 69, 1105 BK, Amsterdam, the Netherlands

Jianbo Zhang
1. Department of Molecular Biology and Microbial Food Safety, Swammerdam Institute for Life Sciences, University of Amsterdam, Amsterdam, the Netherlands
2. Tytgat Institute for Liver and Intestinal Research, Amsterdam Gastroenterology Endocrinology Metabolism, Amsterdam University Medical Center, Location AMC, University of Amsterdam, Meibergdreef 69, 1105 BK, Amsterdam, the Netherlands

Background and objective
Candida albicans is a common yeast found in the human gut, but its genotypic and phenotypic characteristics have been linked to inflammatory bowel disease (IBD), with the hyphal form associated with increased virulence. Previously, over 250 C. albicans isolates from healthy individuals and patients with quiescent IBD (qIBD) were genotyped, showing divergent effects on the integrity of Caco2-derived monolayers. While strain diversity appears to correlate with disease severity, the underlying mechanisms remain unclear. To investigate C. albicans-related pathophysiology in IBD patients, we developed an organoid-derived in vitro gut-fungi coculture model.

Methods and results
We generated colonic monolayers (CMs) from non-lesional colonic resections of ulcerative colitis patients and integrated them into the GuMI microphysiological system. This system promotes in vivo-like C. albicans growth by sustaining a continuous flow of anoxic apical media and oxygenated basolateral media, while maintaining CMs' differentiation. After two days of coculture, the integrity of CMs was assessed through imaging and TEER measurement, and molecular effects were examined using basolateral supernatant analysis and bulk RNA sequencing. Metabolomic analysis of apical supernatants was performed to characterize fungal-secreted factors. Despite the presence of hyphal forms, no obvious damage was observed in the monolayers, and TEER values were not significantly different from (static) controls.

Conclusion / discussion
These preliminary results suggest the need for further analysis to identify fungal-secreted factors and their role in IBD pathogenesis. Additionally, this study demonstrates the successful two-day coculture of fungi with patient-derived primary human CMs, showcasing the model's potential for studying host-mycobiome interactions in the gastrointestinal tract.

Keywords
Gut-on-chip, c.albicans, inflammatory bowel disease, mycobiome, microphysiological systems

Innovative therapeutic strategies targeting NTCP for cholestatic Diseases

Dana Meije
1. Tytgat Institute for Liver and Intestinal Research, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, the Netherlands
2. Amsterdam Gastroenterology, Endocrinology and Metabolism (AGEM), Amsterdam University Medical Centers, the Netherlands.

Stan van de Graaf
1. Tytgat Institute for Liver and Intestinal Research, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, the Netherlands
2. Amsterdam Gastroenterology, Endocrinology and Metabolism (AGEM), Amsterdam University Medical Centers, the Netherlands.

Background
Cholestatic diseases are caused by impaired bile flow, leading to toxic bile salt accumulation in the liver. The Sodium Taurocholate Co-transporting Polypeptide (NTCP) is the main hepatic bile salt uptake transporter and represents a promising therapeutic target. Current therapies, such as NTCP inhibitors like bulevirtide, require daily injections. In collaboration with the Centre for Drug Design and Discovery (CD3) and ProQR Therapeutics, we are investigating an orally avaiblabe NTCP inhibitor (CD3) and an RNA-editing technology, which may provide durable therapeutic effects with less frequent administration (ProQR).

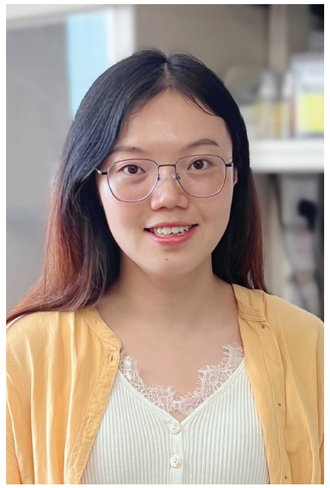
Hypothesis
We hypothesize that inhibiting NTCP can reduce bile salt accumulation and alleviate cholestasis. CD3's small-molecule inhibitor offers a convenient oral treatment, while ProQR's RNA-editing approach enables precise and lasting modulation of NTCP.

Research plan
CD3 Collaboration: In vivo studies are assessing an orally small-molecule NTCP inhibitor in cholestatic mouse models.
ProQR Collaboration: Axiomer™ uses editing oligonucleotides (EONs) to guide endogenous ADAR enzymes for RNA editing. We aim to investigate Axiomer EONs as an approach to specifically modulate NTCP in mouse models of cholestasis.

Anticipated results
The CD3 inhibitor is expected to improve liver function via oral delivery. ProQR's RNA-editing strategy aims for durable NTCP modulation with reduced dosing frequency.

Keywords
Cholestasis, NTCP, small-molecule inhibitor, RNA editing, bile salt modulation

Targeting Hepatic Amino Acid Uptake to Improve Systemic Signaling and Metabolic Diseases



Dandan Wu
Tytgat Institute for Liver and Intestinal Research, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, the Netherlands

Stan van de Graaf
Tytgat Institute for Liver and Intestinal Research, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, the Netherlands

Background and objective
The liver acts as the gatekeeper that controls systemic exposure to intestine and microbiota- derived metabolites. Hepatic transport mechanisms provide opportunities to modulate systemic metabolite signaling. Here, we focus on amino acids as they serve dual functions: as essential precursors for nutrients like glucose and lipid, and as critical regulators of multiple metabolic pathways. Sodium-coupled neutral amino acid transporter 4 (SNAT4) is considered crucial in hepatic neutral amino acid uptake, with its expression predominantly restricted to the liver. However, the physiological and metabolic roles of SNAT4 remain poorly understood.

Methods and results
In vitro, HepG2 cells were subjected to shRNA-mediated knockdown of SLC38A4, the gene encoding SNAT4. In vivo, we are now optimizing a CRISP/cas9 based gene editing system to achieve rapid and efficient liver-specific inactivation of SNAT4 in mice.
In HepG2 cells, SNAT4 knockdown knockdown significantly increased cellular uptake of 14C-methylaminoisobutyric acid (14C-MeAIB) (FC=4), a non-metabolized substrate specific to system A amino acid transporters. Further analyses revealed that compensatory upregualtion of SNAT1 (FC=2.2) and SNAT2 (FC=1.8) expression may contribute to increased uptake. Similar findings were also observed in Huh7 cells.

Conclusion / discussion
SNAT4 knockdown in vitro led to elevated sodium dependent 14C-MeAIB uptake, likely driven by compensatory mechanisms of SNAT1 and SNAT2. The metabolic implications of these changes remain to be elucidated. Future studies in the liver-specific SLC38A4-deficient mouse model will provide critical insights into the role of SNAT4 in hepatic amino acid transport and its broader impact on systemic metabolism.

Keywords
Amino acids, transporter, SNAT4, energy meatbolism, uptake

Dose intensification of vedolizumab is not effective in inducing endoscopic response in Crohn's disease patients with endoscopic primary non-response

Lotte Oldenburg
Amsterdam University Medical Centers, Gastroenterology, Amsterdam, Netherlands

Geert D'Haens
Amsterdam University Medical Centers, Gastroenterology, Amsterdam, Netherlands

Background and objective
Dose intensification of vedolizumab (VDZ) in Crohn's Disease (CD) patients with secondary loss of response has been reported to be effective. Our aim was to investigate the effect of vedolizumab dose intensification in endoscopic non-responders after 26 weeks of standard dosing on clinical and endoscopic remission at week 52.

Methods and results
In the LOVE-CD trial, early and late CD patients with moderate-severe disease activity at baseline endoscopy were treated with VDZ for 52 weeks. Early CD was defined as diagnosis <24 months and late CD as diagnosis >24 months and previous exposure to anti-TNF. All patients underwent an endoscopy at week 0, 26 and 52. Halfway the trial, the study protocol was amended by introducing dose intensification from 300 mg IV every 8 weeks to every 4 week in patients without endoscopic response at week 26. The primary outcome was deep remission, defined as clinical (CDAI ≤150) and endoscopic remission (SES-CD ≤3) at week 52.

In LOVE-CD, eighty-two patients (31.5%) were endoscopic non-responders at week 26 (44 prior to and 34 after the amendment). Baseline characteristics were similar between the dose intensification and standard dosing groups (median SES-CD at baseline 11 (7-17) vs 13 (8-18) resp.). At week 52, the dose-intensified group had significantly higher VDZ serum concentrations at trough (mean 46.4 vs 16.3 ug/ml, p<0.001). However, there was no significant difference in endoscopic remission and clinical remission rates at week 52.

Conclusion / discussion
Dose intensification of VDZ in endoscopic non-responders with Crohn's Disease after 6 months of standard dosing is not effective.

Keywords
Crohn's Disease; treatment response; dose intensification; Vedolizumab; endoscopy

The Enhanced Liver Fibrosis score and Liver Stiffness Measurement as surrogate endpoints in primary sclerosing cholangitis

Tim Midddelburg
Amsterdam UMC, UVA,Gastroenterology and Hepatology, Amsterdam, The Netherlands

Cyriel Ponsioen
Gastroenterology and Hepatology, Amsterdam, The Netherlands

Background and objective
Primary sclerosing cholangitis (PSC) is characterized by progressive fibrotic structuring of the biliary tree that leads to end-stage liver disease. Anti-fibrotic drugs have potential, however, surrogate endpoints to assess efficacy are not validated yet. This study aims to assess the role of Enhanced Liver Fibrosis (ELF) and Liver Stiffness Measurement (LSM) in predicting end-stage liver disease and implementation in clinical studies.

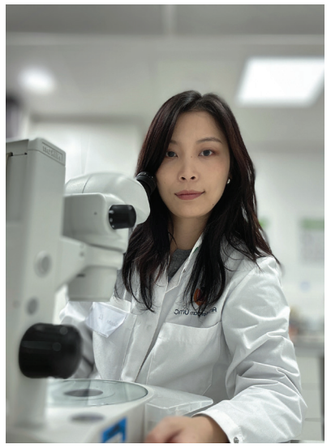
Methods and results
PSC patients from a prospective cohort including annual LSM and biobank sampling were used. ELF score was determined via Siemens ELF test. LSM and ELF results were paired by date and combined with clinical data. For clinical study simulation, a 2 year timeframe was assessed. Outcomes were liver decompensation or transplant-free survival. Cox proportional hazard regression was used to assess independent prediction capacity from LSM and ELF. Model performance was determined by C-statistic.

95 patients with 337 paired ELF and LSM measurement were included. 14 events occurred during a median 4.4 years follow-up. Multivariate analysis showed baseline ELF and change from baseline as independently predictive for event-free survival (HR 9.1, p = 0.009; HR 1937.1, p= 0.009), LSM was not. In a 2-year interval, including 61 patients and 8 events, similar results were found (HR 6.0, p=0.03; HR 16.3, p =0.02). A combined model showed a C-statistic of 0.9, indicating an excellent prediction.

Conclusion / discussion
The combination of baseline and change over time of ELF score exceeds the use of LSM as an excellent predictor for event-free survival and could potentially be a surrogate endpoint for clinical studies in PSC.

Keywords
PSC, fibroscan, ELF, fibrosis, monitoring

Plasma triacylglycerol length and saturation level mark healthy aging groups in humans with endoscopic primary non-response



Weisha Li
Amsterdam UMC Location University of Amsterdam, Laboratory Genetic Metabolic Diseases, Amsterdam, The Netherlands

Georges Janssens
Amsterdam UMC Location University of Amsterdam, Laboratory Genetic Metabolic Diseases, Amsterdam, The Netherlands

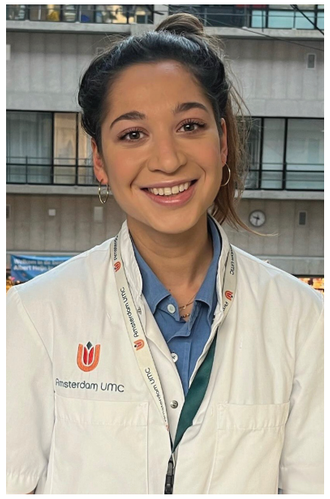
Background and objective
Complex lipids, essential components in biological processes, exhibit conserved age-related changes that alter membrane properties, cellular functions, and are implicated as biomarkers and contributors to longevity and age-related diseases. While physical activity alleviates age-related comorbidities and physical impairments, comprehensive exploration of the underlying biological mechanisms, particularly at the level of complex lipids, remains limited. However, clinical studies suggest that physical activity may counteract these age-related lipidomic changes, presenting a promising avenue for intervention.

Methods and results
We performed lipidomic profiling of plasma from an extensively characterized cohort of young and aged individuals.

Conclusion / discussion
Annotating 1446 unique lipid species across 24 lipid classes we found the most prominent difference in older adults was an accumulation of triacylglycerols (TGs), with lower physical activity levels associated with higher TG levels in plasma and reduced physical functionality. Remarkably, lipid species in the TG class did not accumulate uniformly. Rather, our study unveiled a negative correlation between higher physical activity levels and TGs with shorter chain length and more double bonds in this demographic. Overall, our research highlights that plasma TG length and saturation level can help mark healthy aging groups in humans. These findings deepen our understanding of how aging affects complex lipids, and the influence of physical activity on this process.

Keywords
Aging, healthy aging, lipidomics, human plasma, triacylglycerols, physical activity.

SCT- Delphi Study: Development of a Core Outcome Set for treatment of Sacrococygeal Teratoma



Malou Dongen
Department of Pediatric Surgery, Emma Children's Hospital, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, The Netherlands.

Joep Derikx
Department of Pediatric Surgery, Emma Children's Hospital, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, The Netherlands.

Background
Sacrococcygeal teratoma (SCT) is the most common extragonadal germ cell tumor in neonates. Although typically benign at birth, the risk of transformation and recurrence requires complete surgical removal. Research on SCT is limited by heterogeneity in outcomes, long inclusion periods, and small cohorts, which complicates data synthesis and hinders the development of international guidelines."

Hypothesis
To address the challenges in current SCT research, we aim to develop a Core Outcome Set (COS) using the Delphi method to achieve consensus on key outcomes. This will help standardize outcome reporting, improve the quality of SCT research and enhance clinical care globally.

Research plan
This study follows the COMET criteria and involves three key phases. The first phase involves a systematic review to identify currently reported outcomes for SCT patients following surgical treatment. In the second phase, two parallel Delphi studies will be conducted: one tailored for High-Income Countries (HICs) and another for Low- and Middle-Income Countries (LMICs/LICs). This distinction enables consideration of varying healthcare contexts, including differences in resources and follow-up. Our Delphi study will engage an expert panel, comprising medical specialists from various healthcare disciplines and patient representatives, to prioritize outcomes identified through the systematic review. Following the Delphi process, in the third phase, a final consensus meeting will ratify the core outcome set.

Anticipated results
The study will produce a globally applicable Core Outcome Set for SCT. This COS will include critical outcomes for both high- and low-resource settings. It will provide consistency in outcome reporting and enable comparisons in research and clinical practice across diverse healthcare contexts.

Keywords
Delphi, Core Outcome Set, Sacrococcygeal Teratoma, Qualitative research

Session E

13:30-14:00

Plenary session
't Speuld

Session E | 't Speuld

Michelle Bloem	ACU-PILOT: Acupuncture in children with functional constipation – a pilot study
Veronika Duwel	Close the gap: Advancing Pregnancy Care for People with Pregestational Diabetes
Ryan Aukes	Evaluation of newborn screening for diseases using 3-hydroxy-isovalerylcarnitine (C5-OH) as a marker: systematic review of the literature and evaluation of 17 years of C5-OH screening in the Netherlands
Ting Chen	Liver Sinusoidal Endothelial Cells Affect Lipid Metabolism in Hepatocytes and Form Lipid Droplets Under Steatotic Conditions

ACU-PILOT: Acupuncture in children with functional constipation – a pilot study

Michelle Bloem
1. Department of Pediatric Gastroenterology and Nutrition, Emma Children’s Hospital
2. Amsterdam University Medical Centre location AMC, Amsterdam, The Netherlands

Marc Benninga
1. Department of Pediatric Gastroenterology and Nutrition, Emma Children’s Hospital
2. Amsterdam University Medical Centre location AMC, Amsterdam, The Netherlands

Background
Functional constipation (FC) is common in children and poses a significant burden to patients and healthcare systems. Pharmacological treatment mainly consists of osmotic laxatives. However, poor adherence to oral laxatives is a known common problem and patients often remain symptomatic despite treatment. Therefore, many parents seek help in the form of alternative medicine. Acupuncture has been shown to relieve symptoms in adults with FC. However, research on acupuncture for pediatric FC is limited.

Hypothesis
Evaluate feasibility of acupuncture as a treatment for children with FC (6 to 18 years), based on Rome IV criteria. The primary aim is to determine whether acupuncture can be a feasible intervention for a larger randomized controlled trial (RCT). Secondary endpoints include consent rate, satisfaction, personnel capacity, (serious) adverse events, reduction in symptoms and quality of life.

Research plan
A prospective, non-randomized, multicenter, open-label pilot study will enroll 18 children. Participants will receive 8 acupuncture sessions over ten weeks. Feasibility will be defined by an attrition rate of at least 70% of participants attending 75% of sessions.

Anticipated results
The results will guide the design of a future RCT for pediatric FC. Currently, no standard acupuncture protocol exists for this demographic. Although published data on acupuncture’s effectiveness and safety for FC patients are promising, studies are often of poor quality, and most evidence comes from Chinese studies. Publication bias may affect validity and reliability of these data. Therefore, the aim is to establish a feasible and effective protocol for pediatric FC, helping fill a significant gap in current treatment options.

Keywords
Functional constipation, acupuncture, disorders of brain gut interaction, pilot

Close the gap: Advancing Pregnancy Care for People with Pregestational Diabetes

Veronika Duwel
Amsterdam UMC, Vrije Universiteit Amsterdam, Endocrinology, Amsterdam, The Netherlands

Sarah Siegelaar
Amsterdam UMC, University of Amsterdam, Endocrinology, Amsterdam, The Netherlands

Background
Living with diabetes poses significant challenges, particularly for pregnant people. In the Netherlands, approximately 800 pregnancies are affected with pregestational diabetes (PGDM) every year, requiring strict glucose control to prevent adverse pregnancy outcomes. Despite advancements in diabetes technology, many struggle to achieve recommended glucose targets, facing increased risks of maternal and neonatal complications such as congenital malformations, stillbirth, preterm birth, or hypertensive disorders of pregnancy, compared to women without diabetes.

Hypothesis
This is a first database around pregnancy with PGDM in the Netherlands and a second one worldwide, after United Kingdom. It will contribute to the understanding of diabetes management during pregnancy in the Netherlands, measure current incidence of PGDM and prevalence of adverse outcomes, and allow for monitoring in the coming years.

Research plan
A prospective registry will be established to measure pregnancy outcomes among pregnant people with PGDM in the Netherlands. This national initiative will assess incidence rates, pre-pregnancy care, and technology uptake, comparing outcomes to women without diabetes. The study will utilize comprehensive data collection methods, including patient records, healthcare provider reports, and other existing databases to track maternal, perinatal, and neonatal outcomes.

Anticipated results
Initial findings will include preconception and pregnancy care practices, glucose regulation, incidence rates of complications, and uptake of use of diabetes technology among pregnant women with diabetes. By establishing a national registry the project aims to optimize pregnancy care and improve pregnancy related health outcomes for women with PGDM in the Netherlands.

Keywords
Pregnancy; Registry; Pregestational diabetes; Type 1 diabetes; type 2 diabetes

Evaluation of newborn screening for diseases using 3-hydroxy-isovalerylcarnitine (C5-OH) as a marker: systematic review of the literature and evaluation of 17 years of C5-OH screening in the Netherlands

Ryan Aukes, MSc.
Department of Pediatrics, Division of Metabolic Disorders, Amsterdam UMC, University of Amsterdam, The Netherlands

Prof. dr. A. M. Bosch
Department of Pediatrics, Division of Metabolic Disorders, Amsterdam UMC, University of Amsterdam, The Netherlands

Background and objective
In 2007, the Dutch newborn screening (NBS) program was expanded to include 3-hydroxy-isovalerylcarnitine (C5-OH) as a marker to screen for three inborn errors of metabolism (IEMs): 3-methylcrotonyl-CoA carboxylase deficiency (3-MCCD), 3-hydroxy-3-methylglutaryl-CoA lyase deficiency (HMGCLD) and holocarboxylase synthetase deficiency (HLCSD).

Methods and results
This study evaluates the effectiveness of C5-OH as an NBS marker by using 17 years of Dutch screening data and reviewing the literature on different IEMs detected by elevated C5-OH concentrations and associated concentrations. We analyzed data from 1 315 861 neonates screened in the Dutch NBS program from 2007 to 2023 in order to determine its predictive value (PV). Additionally, we performed a systematic literature review on different diseases detected by NBS programs worldwide in relation to NBS C5-OH concentrations. Of the 126 Dutch neonates referred due to elevated C5-OH concentrations, 46 cases were true positive cases and no missed cases were reported, resulting in a positive predictive value of 38.3% and a negative predictive value of 100%. Strikingly, there was notable overlap between C5-OH concentrations of true and false positive cases. The systematic review showed that C5-OH concentrations of patients with different IEMs reported in literature were insufficiently distinctive to differentiate between these conditions.

Conclusion / discussion
While C5-OH can be used to detect patients with 3-MCCD, HCLSD and HMGCLD, its value is limited by the overlap in C5-OH concentrations between affected and unaffected neonates and among patients with different diseases. This emphasizes the need for improvement of the screening strategy and potentially the use of additional markers to increase its specificity.

Keywords
Newborn Screening, marker, 3-hydroxy-isovalerylcarnitine

Liver Sinusoidal Endothelial Cells Affect Lipid Metabolism in Hepatocytes and Form Lipid Droplets Under Steatotic Conditions

Ting Chen
Amsterdam University Medical Center, Department of Vascular Medicine, Amsterdam, The Netherlands

Onno Holleboom
Amsterdam University Medical Center, Department of Vascular Medicine, Amsterdam, The Netherlands

Background and objective
Dysfunctional liver sinusoidal endothelial cells (LSECs) aggravate metabolic dysfunction-associated steatotic liver disease (MASLD), already from the early stage of MASLD. We aimed to characterize the role of LSECs in regulating lipid metabolism in hepatocytes under steatotic conditions by deploying a co-culture of lipid-laden HepG2 and immortalized LSECs (HLEC), using human aortic endothelial cells (HAECs) as control.

Methods and results
HepG2 received 24-hour pretreatment of 250μM Oleic acid and 125μM palmitate (OA/PA) or BSA, with or without the transwells of HLECs/HAECs above, creating a setting to study paracrine effects and mimicking the space of Disse. The intracellular lipid droplets in both hepatocytes and endothelial cells were stained and measured, and mRNA expression was studied.

Upon OA/PA loading, co-culturing with HLECs resulted in smaller lipid droplets in HepG2 cells and 68% reduced intracellular triglyceride content. In HepG2 treated with OA/PA, lipogenic mRNA expression was inhibited upon co-incubation with HLECs but not with HAECs, including acetyl-CoA carboxylase alpha (ACACA) and sterol regulatory element-binding protein 1 (SREBP1). The gene encoding carnitine palmitoyl transferase 1A (CPT1a) as well as CD36 (lipid transporter) was down-regulated upon co-culture with HLECs. Of interest, lipid droplets volume was upregulated in HLECs when co-cultured with HepG2 cells.

Conclusion / discussion
Co-culturing of hepatocytes with LSECs resulted in a less severe steatotic phenotype of the former cells, a feature that’s absent in the presence of HAECs. These data strongly suggest that LSECs have a protective effects on hepatocytes via a paracrine factor. Future research aims to explore this paracrine LSEC-hepatocyte axis.

Keywords
LSEC, hepatic steatosis, lipid metabolism, co-culture

Amsterdam UMC

Amsterdam Gastroenterology Endocrinology Metabolism